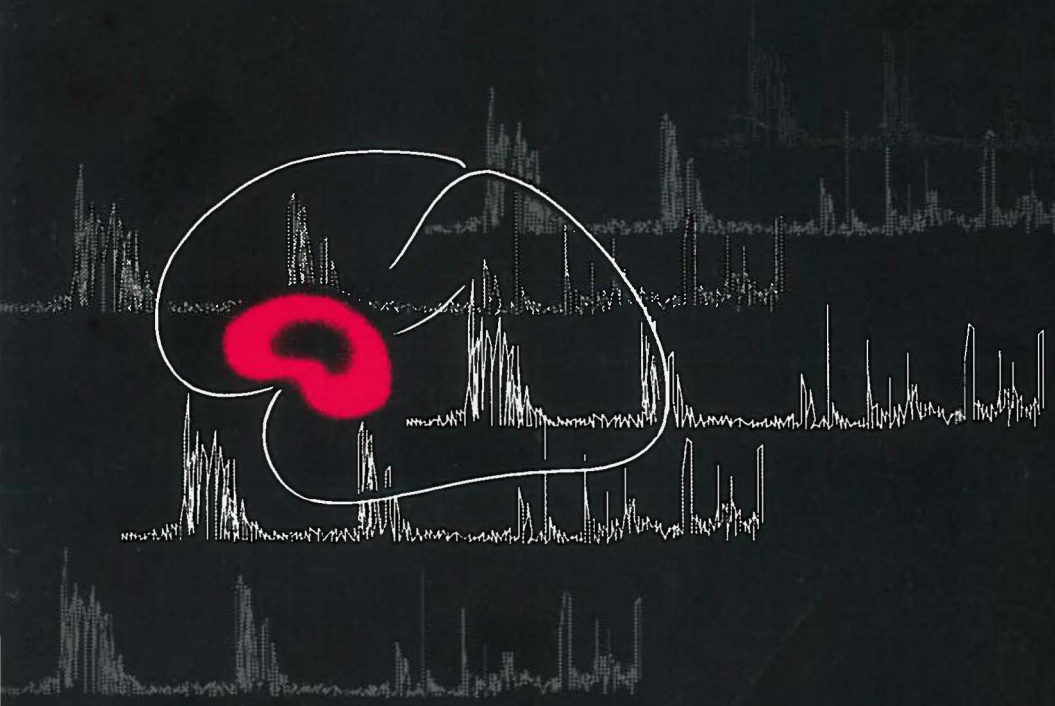
Cerebral Protection in Aneurysm Surgery : Barbiturates, Hypothermia and Neuromonitoring

Belopavlovic, Milan; Buchthal, Anna Barbara

CEREBRAL PROTECTION IN ANEURYSM SURGERY: HYPOTHERMIA, BARBITURATES AND NEUROMONITORING



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CEREBRAL PROTECTION IN ANEURYSM SURGERY: BARBITURATES, HYPOTHERMIA AND NEUROMONITORING

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Stellingen

M. Belopavlovic

I.

"I would be more concerned to know that an experienced neuroanaesthetist was going to be available than to fuss about which neurosurgeon was going to operate". Bryan Jennett, If my son had a head injury. Britisch Medical Journal 1978, 1: 1601-3.

II.

Hersendood dient met transcraniële Doppler metingen te worden bevestigd.

III.

Cerebrale angiographie dient bij voorkeur plaats te vinden bij een patiënt met volledig bewustzijn en zonder algehele anaesthesie.

IV.

Een geruptureerd intracraniëel aneurysma dient als spoedgeval te worden geopereerd, tenzij de patiënt in een te slechte neurologische toestand verkeert.

V.

Bij neurochirurgische patiënten dient systemische arteriële hypotensie met uiterste voorzichtigheid te worden toegepast.

VI.

Wanneer cerebrale vaatspasmen symptomatisch worden behandeld met intravasculaire volume-therapie en geïnduceerde hypertensie, dienen transcraniële Doppler metingen een richtlijn te geven voor de mate en duur van die therapie.

VII.

Keuze van de aard en duur van cerebrale protectie is afhankelijk van de onderliggende oorzaak van de ischaemie.

VIII.

De maximaal beschermende werking van barbituraten tegen de gevolgen van focale cerebrale ischaemie, wordt verkregen bij doseringen die ver liggen boven de dosis, noodzakelijk om een iso-electrisch EEG te verkrijgen.

IX.

Bij patiënten met hypothermie dient uiterste zorgvuldigheid in acht te worden genomen wanneer beëindigen van een cardiopulmonale en cerebrale reanimatie wordt overwogen.

X.

Excessief separatisme van medische specialismen is niet in het belang van de patiënt.

XI.

"Geen bezwaar tegen narcose" is een onbevoegde uitspraak bij de internistische pre-operatieve beoordeling.

Stellingen

A. Buchthal

I.

De practische waarde van bewakingsapparatuur hangt af van de gebruiker.

II.

De routinematige toepassing van de postoperatieve intracraniële drukmeting is door de direkte beschikbaarheid van de CT-scan obsoleet geworden.

III.

Inhalatie-anaesthetica zijn in principe niet geschikt voor de neuro-anaesthesie.

IV.

De bescherming van de hersenen door barbituraten is onafhankelijk van hun vermogen tot vermindering van hersenoedeem en tot verlaging van de intracraniële druk.

V.

Farmaca, die het cerebrale metabolisme aanzetten, dienen bij neurochirurgische patiënten slechts op bijzondere indicatie te worden aangewend.

VI.

Cerebrale vaatspasme en de gevolgen daarvan vormen tegenwoordig het belangrijkste probleem bij de behandeling van patiënten met een subarachnoidale bloeding.

VII.

De Doppler sonografie, als dagelijkse routine-meting ter beoordeling van cerebrale vaatspasme, zal voor de neurochirurg een belangrijk hulpmiddel worden om het tijdstip van operatie bij patiënten met een intracraniëel aneurysma te bepalen.

VIII.

Een neuro-anaesthesist, die volledig is belast met de zorg voor neurochirurgische patiënten, is een aanwinst voor een neurochirurgische kliniek.

IX.

Barbituraten zijn onwerkzaam bij de behandeling van gevolgen van globale cerebrale ischaemie.

X.

Een iso-electrisch EEG onder invloed van barbituraten vertegenwoordigt geen toestand van maximale functionele cerebrale depressie.

XI.

Neurochirurgie zonder adequate "neuro-monitoring" is te vergelijken met hartchirurgie zonder electrocardiografische bewaking.

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ANNA BARBARA BUCHTHAL

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CHAPTER I

General introduction

Ruptured intracranial aneurysms present one of the greatest challenges in neurosurgery today. Primary subarachnoid haemorrhage (SAH) has an incidence of 8.7 per 100,000 population per annum in The Netherlands, comprising about 5% of strokes (70, 71). Moreover, aneurysmal SAH occurs predominantly in the younger sector of the population, 33.3% of cases coming for surgery in Groningen during the period 1977-1987 being under the age of 40 and 90% being under the age of 60 at the time of presentation. Approximately one third of all patients experiencing SAH die or are neurologically disabled following the initial haemorrhage (89); 10-15% die within hours of aneurysmal rupture and may not reach the neurosurgeon (104).

For patients who reach surgery, the operative mortality has been variously reported as ranging between 5 and 15%. The last few years have seen some significant advances in the perioperative management and in microsurgical techniques which have been accompanied by a reduction in operative mortality to as low as 2%.

The episode of SAH itself is accompanied by disruptions in cerebrovascular haemodynamics which may be severe and predispose to neurological damage. Broadly, these disruptions take two forms. Cerebrovascular autoregulation becomes defective so that cerebral perfusion, which is normally held constant in the face of a changing systemic arterial blood pressure, now becomes pressure dependent in the affected areas (217). This renders those areas susceptible to hypoperfusion or ischaemia as a result of a reduced arterial blood pressure on one hand and to the formation of vasogenic cerebral oedema in the face of a raised arterial pressure on the other. At the same time, cerebral arterial vasospasm may develop within a few days of SAH (72). Cerebral vasospasm following SAH may be localised or very extensive and can persist for up to four weeks; it can lead to the formation of ischaemic cerebral oedema which itself further embarrasses local cerebral perfusion, leading to infarction, while intracranial pressure may be raised to such an extent as to result in tentorial herniation in extreme cases. Cerebral vasospasm is responsible for a major proportion of the morbidity associated with cerebral aneurysm cases, (178), whether they are subjected to surgery or not. Vasospasm may be provoked by surgical manipulation even when it was not apparently present preoperatively and can persist into the postoperative period for a variable period of time.

Unlike stroke, however, which is the result of cerebral haemorrhage, thrombosis or embolism in the presence of underlying vascular or systemic pathology, vasospasm is intrinsically a transient phenomenon, persisting at most

for about four weeks, so that the outlook for these patients is good if there is no permanent ischaemic damage and the aneurysm can be repaired before recurrent haemorrhage occurs. For this reason, the attention of the neurosurgeon and the neuroanaesthetist has been drawn in recent years to exploring the possibilities of preventing the development of cerebral vasospasm or alleviating it one one hand and of minimising the effects of cerebral ischaemia resulting from it on the other.

There have been two principal approaches to the reduction of the morbidity and mortality associated with cerebral vasospasm in aneurysm patients. The first concerns the timing of the operative intervention. It is widely accepted that operative intervention between the fourth and the tenth day post-SAH is followed by a higher complication rate than is intervention after the tenth day (84, 89). However, waiting for ten days before surgical intervention can be a difficult decision to make in view of the risk of recurrent SAH, and perhaps death or devastating neurological damage in the meantime: the incidence of recurrent haemorrhage in the first two weeks after the initial aneurysm rupture is 20% (235). Moreover, the promotion of adequate cerebral perfusion in the face of cerebral vasospasm by means of intravascular fluid loading and arterial hypertension (53, 77, 94, 100, 140, 165, 196) is fraught with danger in a patient where the aneurysm remains unclipped.

These considerations have given rise to a trend, which has been growing recently, for early surgery, i.e., within 72 hours of SAH, provided that there is no evidence of vasospasm at that time. While early surgery certainly does not carry a lower operative risk than late surgery, it should contribute to the reduction of mortality and morbidity resulting from recurrent haemorrhage between the third and the tenth day post-SAH.

Another approach to the problem of vasospasm is pharmacological. A large variety of drugs has been tried in the search for a remedy for vasospasm. The most recent group to be assessed clinically is the calcium channel entry blockers, which may be effective in reducing the incidence of vasospasm when given before its onset but are not effective in alleviating established vasospasm (6, 12, 13, 102, 159). These drugs will not be considered further in this thesis.

The problem of protecting the cerebral aneurysm patient from cerebral ischaemia and its effects during surgery are compounded by the difficulty of clinical neurological assessment under general anaesthesia. The most sensitive signs of ischaemia - disorientation, confusion, drowsiness and, later, motor deficit - cannot be observed under anaesthesia. Two approaches have recently been applied to this problem. The first approach involves increasing the resistance of the brain to the effects of ischaemia while the second involves the employment of sensitive detection techniques to allow early detection and enable remedial action to be taken before neurological damage occurs. This thesis is devoted to these two

aspects of cerebral protection in aneurysm surgery. In Chapter II, the use of hypothermia in neurosurgery is discussed. The ability of the brain to survive over 35 minutes of circulatory arrest at 28°C with minimal ultimate neurological damage is illustrated with a case report. Moderate hypothermia has been used throughout the cases presented in this thesis, sometimes in combination with additional surgical, anaesthetic or monitoring techniques. Chapter III.1 reviews the experimental evidence for cerebral protection from ischaemia with larger doses of barbiturates, discusses their mechanisms of action and their use in clinical practice at the time when we first began to use them for cerebral aneurysm patients. The latter occasion is described in Chapter III.2 and led to the development of a technique for prophylactic loading with pentobarbitone together with hypothermia. Chapter III.3 presents the clinical results of the prophylactic use of high doses of pentobarbitone in a series of 23 consecutive cases in which the aneurysm was clipped. The results are compared to those of 69 cases where barbiturates were not used and demonstrate cerebral protection from focal cerebral ischaemia by barbiturates in human beings. Chapter IV describes the intraoperative employment of electrophysiological monitoring techniques. In Chapter IV.1, the use of a monitoring device based on a single channel electroencephalogram (EEG) during high dose barbiturate therapy is discussed. The limitations of an EEG-derived signal in providing neurological assessment under these conditions are evident. In contrast, the persistence of event related or evoked potentials is noted. In Chapter IV.2, the potentially devastating sequelae to intraoperative aneurysmal rupture, even in the presence of prophylactic barbiturate loading, are illustrated by a case report. A second case report describes a microsurgical technique of temporary vascular occlusion proximal to the aneurysm which reduces this risk to a minimum, used together with a technique for monitoring function of the cortical area made ischaemic by the occlusion. A third case report illustrates the practical feasibility of using the techniques of temporary vascular occlusion and monitoring with somatosensory evoked potentials (SEPs) in the presence of high doses of barbiturates. Chapter IV.3 describes the technique of temporary vascular occlusion with SEP monitoring in detail, illustrated by five preliminary cases. The limitations of the monitoring technique are discussed. Finally, in Chapter IV.4, 25 cases of temporary arterial occlusion with SEP monitoring are reviewed and the use of the SEP to indicate a "safe" period of cerebrovascular occlusion is evaluated as far as possible. Our overall conclusions are summarised in Chapter V.

CHAPTER II

HYPOTHERMIA

CHAPTER II.1

General introduction

Until the present time, the most widely used single technique for achieving cerebral protection in clinical practice has undoubtedly been hypothermia. Moderate hypothermia, at temperatures of 27°C to 30°C, where reliance is placed on continuing spontaneous cardiac action, is readily achieved by surface cooling following appropriate premedication to prevent shivering. During profound hypothermia, at temperatures below 27°C and sometimes below 20°C, the circulation must be maintained by extracorporeal means and a limited period of circulatory arrest can be tolerated when this is necessary to aid the surgeon. The definition of such a "safe" period of circulatory arrest, during either moderate or profound hypothermia, has been the subject of extensive discussion and, to a lesser extent, remains so today. Profound hypothermia with cardiopulmonary bypass is routinely used today for cardiac surgery in all major cardiothoracic centres. While both moderate and profound hypothermia were introduced for cerebrovascular surgery in the 1950's and were used in the 1960's (4, 30, 39, 40, 65, 88, 106, 107, 209, 225, 262), however, profound hypothermia is not used today and moderate hypothermia is used only in very few Neurosurgical centres.

One of the centres where moderate hypothermia remains in routine use for cerebrovascular surgery today is the Neurosurgical Clinic of the Academisch Ziekenhuis, Groningen. The reasons for the persistence of the technique here while it has long been abandoned in most other Neurosurgical institutions were perhaps related to surgical technique and convenience rather than to cerebral protection in the first instance. A reduction in body temperature of 8° to 9°C leads to a substantial reduction in brain size as well as a reduced production of cerebrospinal fluid. In addition, there is an anticoagulant effect resulting from slowed enzymic action while bleeding is reduced in connection with a markedly slowed pulse rate and a moderately reduced arterial blood pressure and cerebral blood flow. In these circumstances, surgical access to the arteries at the base of the brain is greatly facilitated, particularly when a frontal approach is used. Cerebral blood low falls by 6.7% per degree Celsius drop in body temperature while the arteriovenous oxygen difference remains unchanged (133). There is no evidence of accumulation of acid metabolites indicative of cellular hypoxia (41, 127). The added bonus for the patient is a reduction in cerebral oxygen consumption by

approximately one half at 28°C, as determined in dogs (174, 133), so that the tolerance of ischaemia by the brain is correspondingly increased. The rates of ATP depletion and lactate accumulation in complete global ischaemia produced by decapitation are slowed by 40% at 30°C as compared to those at 37°C in dog brain (134).

The capacity of dogs to survive a period of over 15 minutes of circulatory standstill at a body temperature of 20°C was demonstrated in 1950 by Bigelow et al (24), and survival without neurological deficit after 10 to 15 minutes' standstill at 19°- 25°C was observed in 1951 by Boerema et al (28). Cerebral protection by hypothermia during circulatory arrest in the intact dog was subsequently demonstrated by Pontius et al (163). The dogs survived 30 minutes of standstill at 25°C to 31 °C without apparent neurological damage. Lougheed and Kahn concluded that dogs can tolerate a single period of complete afferent vascular occlusion to the brain of upto 15 minutes or repeated episodes of upto 12 minutes' duration at 23.6°C - 25°C (106). Marshall et al found that normothermic dogs under pentobarbitone anaesthesia died within 14 minutes of arterial occlusion to the brain while animals at 23°C - 26°C all survived for at least 45 minutes (118). The rabbits of Hirsch et al survived increasing periods of complete global ischaemia at progressively lower temperatures: 10 minutes at 36°C, 25 minutes at 28°C and 40 minutes at 22°C (73).

Monkeys appear to tolerate hypothermia badly, even in the absence of an ischaemic insult. Although White et al succeeded in demonstrating recovery in the monkey after one hour of global ischaemia at 5°C - 8°C (234), three separate studies in which hypothermia was induced 30 minutes after transorbital middle cerebral artery occlusion failed to demonstrate any beneficial effect: rather, a detrimental effect was seen (131, 205, 287). However, while other means of cerebral protection are effective in a similar monkey model after such a time delay (184), the induction of hypothermia 30 minutes postocclusion may be too late to achieve protection as cerebral oedema formation supervenes within this time (16).

In man, Lam et al concluded that 30 minutes of cardiac arrest could be tolerated at 25°C during cardiac surgery (97) and Seelye et al considered a maximum of 55 minutes' arrest to be "safe" at 23°C (183). During cerebrovascular surgery, Botterell et al considered 8 minutes of complete arterial occlusion to the brain to be "safe" at 28°C (30), while Karlsberg and Adams also allowed less than 10 minutes at 28°C - 30°C (88).

When then, in view of the advantages it appears to offer to both the surgeon and the patient, is hypothermia not in more widespread use in neurosurgery today? Its employment is a little more time consuming, requires a little more care during rewarming immediately postoperatively and, perhaps the strongest argument, several centres have reported that their clinical results were not better when using

hypothermia, but, if anything, were worse (66, 127). With the sophisticated patient monitoring equipment available today, any additional morbidity associated with the use of hypothermia itself has not been evident in our experience with over 250 cases of cerebral aneurysms, arteriovenous malformations and pituitary tumour cases where it has been employed in Groningen during the period covered by this thesis. Nevertheless, the overall clinical results of our cerebral aneurysm cases, described in Chapter III.3, are not obviously better than those reported by other centres in the same period. This is a valid observation and calls for some comment on the mechanisms responsible for cerebral ischaemic damage in these patients. Hypothermia does indeed protect the brain from the effects of a degree of cerebral ischaemia, but the protection is no longer effective after the patient is rewarmed. The commonest cause of cerebral ischaemia in aneurysm patients is cerebral vasospasm. This, however, generally has a much longer time course than the duration of the operation and may become manifest only postoperatively after the patient has been rewarmed. Effective cerebral protection in aneurysm patients therefore demands either a means of preventing cerebral vasospasm or, in the absence of this, the employment of a protection technique whose time course parallels that of vasospasm. We shall see in subsequent chapters that some progress has been made in both of these directions.

Other aspects of cerebral protection in cerebral aneurysm cases are considered in the chapters which follow. All the work, however, was carried out on a background of hypothermia, which was employed throughout the material presented in this thesis and which, as we shall see, has allowed the development and use of a technique which cannot be used in the same way at normal temperatures.

Turning again to the potential hazards of hypothermia, it is well known among those who handle hypothermic patients that they tolerate sudden and massive blood loss very poorly. The case report which follows describes events in such a case. At the same time, there are several reports in the literature of small children surviving submersion in cold water, for example, for 40 minutes, and found with a body temperature of 24°C, without apparent permanent neurological damage (186, 240). These reports, as well as our own case. illustrate that "you should never give up in the cold".

CHAPTER II.2

Cardiac arrest during moderate hypothermia for cerebrovascular surgery

Anaesthesia, 1980, Volume 35, pages 235-245

M. Belopavlovic and A. Buchthal

Summary

A case of cardiac arrest during moderate hypothermia and profound hypotension following rupture of a cerebral aneurysm is described. The patient survived with few neurological sequelae directly attributable to the period of cerebral ischaemia. The protective effect of hypothermia in the prevention of neurological damage is illustrated as are the difficulties of resuscitation.

All cerebrovascular surgery in this department has been carried out under moderate hypothermia (27-29°C) for the last 15 years, often together with induced hypotension, without any complications attributable to the use of hypothermia. However, the potential hazards of hypothermia are much increased by hypotension particularly when this is due to uncontrolled haemorrhage. Cardiac resuscitation under these conditions can present formidable problems as the responsiveness and reserve of the cardiovascular system are severely impaired.

Case history

A women, aged 44 years, was admitted to the Neurosurgical Unit 5 days after a subarachnoid haemorrhage. This had been accompanied by drowsiness, restlessness and dysarthria. There were no neurological signs on admission; there was no relevant past history. Seldinger angiography revealed a saccular aneurysm at the bifurcation of the right internal carotid artery.

Surgery was performed 8 days later. The patient was premedicated with atropine, pethidine, promethazine and chlorpromazine 45 min before further Seldinger angiography. This was followed by regional cerebral blood flow measurement with ^{133}Xe which showed a low mean value of 37 ml/min/100 g brain tissue. Anaesthesia was induced with pancuronium 2 mg, thiopentone 300 mg, pethidine 100 mg and suxamethonium 100 mg; after tracheal intubation anaesthesia was continued with pancuronium 6 mg, pethidine 200 mg and ventilation with 33% O_2 67% N_2O and 2-3 cm H_2O of positive end-expiratory

pressure (PEEP). After placement of central and peripheral venous lines, oesophageal and nasopharyngeal temperature probes and an oesophageal stethoscope, the patient was moved to the waterbath in a supine position with 10° head up tilt. End-tidal CO_2 concentration was monitored using a capnograph and arterial pressure via the Seldinger catheter. Two per cent CO_2 was added to the inspired gas mixture during the surface cooling with iced water at 10°C. Cooling was continued to an oesophageal temperature of 32·5°C. The cold water was then drained out and lumbar puncture performed through a hatch in the bath.

A right frontal craniotomy was performed. After the bone flap was raised the aneurysm was localised by further angiography which showed marked vasospasm. One hundred and twenty ml of cerebrospinal fluid were drained after the dura was opened. The aneurysm was then exposed by surgical retraction. A sodium nitroprusside infusion was started at 80 μg/min because the systolic blood pressure had increased to 160 mmHg; after 5 min this was reduced to 24 μg/min since the arterial pressure had decreased to 95 mmHg. The systolic arterial pressure was allowed to decrease to 50 mmHg during dissection of the aneurysm. The oesophageal temperature at this time was 29°C and the central venous pressure (CVP) was 4 mmHg with reference to the right atrium. There was then a sudden profuse haemorrhage of 1½-2 litres as the aneurysm ruptured. The nitroprusside infusion was immediately discontinued, ventilation continued with 100% O_2 and warmed blood and plasma infused under pressure. The systolic blood pressure fell to 20 mmHg; bradycardia with extrasystoles was followed by asystolic cardiac arrest. Effective external cardiac massage was carried out while 3 litres of blood and 3·25 litres of plasma were given. The aneurysm was coagulated after a few minutes and haemorrhage stopped but the heart was still in asystole. Resuscitation was continued with external cardiac massage, isoprenaline. calcium, bicarbonate, andrenaline and a dopamine infusion without success. An attempt was therefore made to rewarm the patient with warm water but, since to continue massage on a floating patient was clearly impossible, this was abandoned and the thoracic surgeons were called to perform thoracotomy to allow local rewarming of the heart and internal massage. However, after 35 min of asystole, ventricular fibrillation occurred as the patient was moved out of the waterbath on to an operating table and defibrillation was successful at the second attempt. This was followed by nodal tachycardia at 120/min. After 10 min the systolic blood pressure was 50 mmHg and the CVP 16 mmHg. The patient had remained a good colour throughout. Surgery was resumed as the systolic blood pressure increased to 85 mmHg; the oesophageal temperature at this time was 28°C. The brain was slack and showed no sign of oedema and the pupils were small and equal. Ventilation was continued by hand with 100% O_2 as decreased compliance and raised CVP were noted together with an arterial oxygen tension (PaO_2) of 8 kP on 50% O_2. One and a quarter hours after cardioversion the

arterial pressure was 130/70 and the pulse rate 70/min. The patient was not rewarmed.

An epidural transducer was placed in one of the craniotomy burr holes during closure. The patient began to move and breathe spontaneously towards the end of surgery and left sided facial seizures were noticed. She was transferred to the intensive therapy unit postoperatively with a temperature of 29°C and was ventilated overnight with 50% O_2 in air and 6 cm H_2O Peep without active rewarming. Postoperatively the CVP was 22 mmHg and a chest X-ray showed pulmonary oedema which was treated with frusemide when the temperature had risen to 32°C. The chest X-ray the following morning was clear. the heart reverted to sinus rhythm spontaneously as the patient rewarmed.

Left sided seizures became persistent about 6 hours postoperatively as the patient's temperature approached 37°C. As these were not controlled by phenytoin or diazepam, 1 g thiopentone was given followed by an infusion of 36 mg/h for 8 hours. The intracranial pressure (ICP) was less than 3 mmHg immediately postoperatively; it was monitored continuously and remained low. The following morning the patient was awake and was extubated. She was aphasic and had a left hemiplegia. The pupils were equal. The epidural transducer was left in place for 3 days; during this time the pressure never exceeded 7 mmHg.

The aphasia disappeared after 3 days; the patient was discharged 13 days postoperatively with a residual weakness of the left arm and a frontal syndrome. After 5 months the frontal syndrome and the weakness of the left arm were both mild and continuing to improve.

Discussion

Hypothermia is well known to protect the brain from the effects of ischaemia (163). At 28°C cerebral metabolic rate is about 50% of that at 37°C and 8-9 min of total circulatory arrest are considered to be safe.

Siebke et al. (186) reported a case of a 5-year-old boy who was submerged in ice cold water for 40 min and survived without any long term neurological sequelae; his rectal temperature on admission was 24°C. Other groups of investigators (166,48,22) reported good results when hypothermia was induced in patients promptly after resuscitation from cardiac arrest and recommended its use in this situation. Barbiturates are also known to protect the brain from the effects of ischaemia (192, 17), and are now being given to patients as soon as possible after restoration of the circulation following cardiac arrest (36). Barbiturates and hypothermia have both been used after episodes of cerebral ischaemia in order to minimise the development of cerebral oedema which impairs the cerebral circulation and results in secondary hypoxic brain damage. They have been used together only occasionally in head injury patients (189).

Our patient survived 45 min of severe, but not comnplete, brain ischaemia with relatively few neurological sequelae; the sequelae may be attributable more to surgical interference and vasospasm than to cardiac arrest and the period of cerebral ischaemia following it. The presence of moderate or severe vasospasm pre-operatively is known to be associated with a reduced cerebral blood flow and with poor results and focal motor deficits postoperatively. There was a notable lack of obvious brain oedema following resuscitation and the ICP remained low indicating the absence of global cerebral oedema which might have been expected to develop during the first few days postoperatively. Continuous epidural pressure monitoring has been used routinely following intracranial surgery in this unit for the past 5 years and has made a useful contribution to the management of these patients (21,15,121). Epidural pressures have been found to correlate well with intraventricular pressures by several authors. Coroneos et al. (46) found that epidural pressures were satisfactory 24-48 hours postoperatively but over-read intraventricular pressures (by 8-10 cmsH_2O) after this time. Turner et al. (228) found good agreement between the two techniques when the ICP was raised; the epidural pressure never remained low when the intraventricular pressure was high.

The development of a marked and persistent frontal syndrome is remarkable in view of the fact that this region is known to be one of the least susceptible to the effects of hypotension. The frontal cortex has been found experimentally to reoxygenate at very low perfusion pressures and to have the highest tissue oxygen tensions post-ischaemia (148). This patient, however, had an abnormally low cerebral blood flow preoperatively so that the effects of surgical retraction together with prolonged, systemic hypotension might have been much more severe in the frontal region.

An aneurysm can rupture during manipulation under hypothermia as easily as it can at normal temperatures; after this has occurred, it may only be possible to clip or coagulate it under conditions of virtual circulatory arrest. Cardiac resuscitation at these temperatures, however, presented considerable problems. The myocardium is severely depressed, relatively unresponsive to inotropic stimulation by catecholamines and intolerant to acute volume loss and overload. A volume of over 2 litres in excess of the blood loss infused during the period of asystole and cardiac massage resulted in acute heart failure with a very high CVP. The peripheral vessels are similarly unresponsive to volume depletion and to vasocontrictors and the effects of nitroprusside are much prolonged.

CHAPTER III

BARBITURATES

CHAPTER III.1

Barbiturate therapy in cerebral ischaemia

Anaesthesia, 1980, Volume 35, pages 235-245

M. Belopavlovic and A. Buchtal

Summary

Experimental and clinical studies of the protective effect of barbiturates in cerebral ischaemia are reviewed. Their action in protecting the brain from the effects of ischaemia is related to their action as anaesthetic agents and probably to the depression of neuronal function and metabolism but is incompletely understood. Their effect is dose related. Early administration is likely to be crucial to the success of barbiturate therapy as secondary events following an episode of cerebral ischaemia can lead to irreversible brain damage within 2-3 h. A potential collateral circulation appears to be essential for the protective effect of barbiturates. There may be a possibility of partly overcoming time delays in administration by giving larger doses of barbiturates.

Much attention has recently been focussed on brain resuscitation after episodes of cerebral ischaemia such as cardiac arrest and head injuries, especially since it is now clear that a substantial degree of brain damage occurs not at the time of the initial insult but develops secondarily during the ensuing hours and may therefore be preventable.

On the other hand, protective measures taken electively before a time of special risk to the cerebral circulation have potential application in carotid and cerebrovascular surgery, cardiac surgery with or without cardiopulmonary bypass and in Caesarean section. To date, only hypothermia has been used extensively for this purpose; in cerebral aneurysm surgery, however, severe vasospasm associated with cerebral ischaemia and often followed by cerebral oedema remains a major problem.

A number of factors have recently contributed directly or indirectly to better

management of patients with cerebral oedema, to improve neurological status and reduction of complications following intracranial surgery and head injuries. The use of a microscope for cerebrovascular surgery with gentle, controlled retraction of the brain can reduce retraction ischaemia and tissue damage; suitable posture of the patient and choice of anaesthetic technique, including the use of hypothermia and controlled hypotension, also contribute by facilitating surgery. Hyperventilation, corticosteroids and infusion of mannitol are routinely employed to control intracranial pressure; continuous monitoring of intracranial pressure and computerised tomography are valuable adjuncts to their use. The pathogenesis of ischaemic damage is also now better understood in terms of cerebral haemodynamics and metabolism and their relationship to intracranial pressure and cerebral oedema.

In addition to hypothermia and barbiturates, various pharmacological agents have been reported to have a beneficial effect in experimental cerebral ischaemia. These include gamma hydroxybutyrate and its lactone (191), aspartate, glutamine, oxaloacetate (160) and aminophylline (180).

Since 1951, barbiturates have been known to depress the cerebral metabolic rate for oxygen ($CMRO_2$) and cerebral blood flow (CBF) (233). It is, however, still not certain whether the protective effect of barbiturates in cerebral ischaemia is a direct and sole result of metabolic depression. Halothane, which causes a similar degree of $CMRO_2$ depression, exacerbates cerebral oedema and infarction following focal cerebral ischaemia (193, 130). This effect is accompanied by biochemical evidence of brain tissue hypoxia (136) and is associated with a substantial increase in CBF. In contrast, diazepam, which has some protective effect in hypoxia (201) causes no significant depression of $CMRO_2$ (41). The depression of $CMRO_2$ produced by barbiturates is accompanied by a marked shift of oxygen utilisation away from the citric acid cycle towards the pentose phosphate pathway (67) similar to that normally seen in hypoxia; however, under the influence of barbiturates this occurs without any biochemical changes indicative of tissue hypoxia (96).

The $CMRO_2$ can be depressed to a minimum of 45% of the awake, control value by thiopentone. A similar degree of metabolic depression is produced by cooling to 28°C. This metabolic rate is close to the minimum required to maintain cellular integrity (47) at normal temperatures. This degree of neuronal depression produced by thiopentone is accompanied by an isoelectric EEG.

Evidence for barbiturate protection of the brain in ischaemia

The beneficial effects of barbiturates in cerebral ischaemia are now well established in experimental models of both focal and global brain ischaemia and in biochemical terms. This evidence is summarised in Smith's excellent review (192).

Yatsu (238) demonstrated that rabbits given methohexitone recovered rapidly from five minutes' exposure to 4% O_2 while the mean arterial pressure (MAP) was reduced to 30-35 mmHg with trimetaphan and the EEG was isoelectric. All barbiturate-treated animals survived without any neurological deficit while untreated animals either died or developed severe neurological deficits.

Secher & Wilhjelm also demonstrated increased survival times of mice pretreated with barbiturates and subjected to 5% oxygen (182).

Some impressive results have been obtained using middle cerebral artery (MCA) occlusion as an experimental stroke model in nonprimates. Easy access to the middle cerebral artery is obtained via a transorbitol approach. Smith et al. (193) found that pretreating dogs with 56 mg/kg pentobarbitone almost eliminated cerebral infarction and neurological deficit following permanent internal carotid and MCA occlusion as assessed after 7 days. This dose of pentobarbitone was accompanied by an iso-electric EEG. Forty mg/kg thiopentone given either before or 15 min after occlusion together with light halothane anaesthesia was equally effective. Occlusion in untreated animals resulted in much larger infarcts under deep than under light halothane anaesthesia; most of these animals developed severe neurological deficits (Table 1).

Table 1. Neurological and pathological sequelae of permanent internal carotid and middle cerebral artery occlusion in dogs. From Smith (193) with permission of the American Heart Association Inc.

Anaesthetic	Average neurological scores over 7 days	Mean percentage of right hemisphere infarcted after 7 days
Light halothane	1·1±0·4 (SE)	10·8±5·2 (SE)
'Awake'	1·0±0·3	9·6±7·4
Deep halothane	2·4±0·3	28·2±9·9
Deep halothane - hypotension	2·2±0·6	34·1±7·7
Pentobarbital pre-occlusion	0	1·4±0·8
Light halothane + thiopental pre-occlusion	0·05±0·05	2·7±2·5
Light halothane + thiopental post-occlusion	0	0·1±0·1

Other studies include those of Hoff et al. on dogs (76), Levy's work on gerbils (100) and Michenfelder & Milde's work on a variety of animals (132). The latter authors point out the unsuitability of non-primates for such studies as their collateral cerebral circulation is even more variable than it is in primates. However, even in monkeys the effects of MCA occlusion are extremely variable, the size of the resulting infarct ranging between 0 and 100% of the hemisphere (132).

The results obtained with primate models, such as those of Hoff et al. (75), might be expected to depend on whether barbiturates were given before or after

Table 2. Focal ischaemia models in primates.

Reference	Species	Procedure	Barbiturate	Dose	Timing	% hemisphere infarcted		After time
						Untreated	Barbiturates	
100	Baboon	Permanent MCA occlusion	Pento-barbitone	60 mg/kg	5 min before occlusion	14·9	8·4	7 days
	Baboon	Permanent MCA occlusion	Pento-barbitone	90 mg/kg	5 min before occlusion	14·9	4·3	7 days
	Baboon	Permanent MCA occlusion	Pento-barbitone	120 mg/kg	5 min before occlusion	14·9	1·6	7 days
180	Squirrel monkey	MCA occlusion for 2 h	Pento-barbitone	40 mg/kg	Pre-occlusion	17·0	6·0	48 h
132	Java monkey	Permanent MCA occlusion	Pento-barbitone	14 mg/kg + 7 mg/kg/2 h	30 min after occlusion for 42 h	18·8	2·0	7 days
144	Rhesus monkey	MCA embolisation (ketamine anaesthesia)	Pento-barbitone	4 mg/kg/h × 12 h	Within 30 min after occlusion	(42-53)	(15-28)	5 days or more

MCA = middle cerebral artery.

the occlusion, the duration of the arterial occlusion and of the experimental observations and the use of adequate cardiovascular and respiratory support. Most of Hoff's baboons who received the highest dose of barbiturates but no support died despite the small size of the cerebral infarct.

Some of the results of experiments on primate stroke models are summarised in Table 2.

Moseley (144) gave barbiturates to rhesus monkeys within 30 min after MCA embolisation and concluded that their protective effect was greatest in areas of potential collateral circulation and least where the collateral circulation was minimal or absent.

Smith & Marque (194), using a cold-injury model of focal cerebral oedema in dogs, found Thalamonal with nitrous oxide to be as effective as pentobarbitone in reducing oedema.

Safar et al. (177) used a model of global brain ischaemia developed by Nemoto et al. (147). Various doses of thiopentone were given to rhesus monkeys at different times following 16 min of complete, global brain ischaemia. This was produced by inflating a tourniquet round their necks to 1500 mmHg while the MAP was reduced to 50 mmHg with trimetaphan. They were allowed to breathe spontaneously as soon as possible after the ischaemic episode and were assessed on a neurological deficit scale after 7 days of intensive care (Table 3).

Table 3. Data from Safar et al. (177) with permission.

Thiopentone dose	Given post-ischaemia after delay of: (min)	Neurological deficit score % after 7 days	Number of monkeys
None		53	10
90 mg/kg	5	0	5
90 mg/kg	15	18	5
None: IPPV 48 h post ischaemia		16	4
120 mg/kg	60	7	5
None: IPPV 48 h + repeated hypertension		46	4

Control monkeys had a mean neurological deficit score of 53% whereas those who received 90 mg/kg thiopentone 5 min post ischaemia made a complete recovery. However, 90 mg/kg thiopentone given 15 min post ischaemia was no more effective than 48 h artificial ventilation without barbiturates. The fact that untreated rhesus monkeys can survive 15 min of complete, global ischaemia with no detectable neurological deficit when assessed after 7 days, provided that they are given adequate care post ischaemia, emphasises the species differences between monkeys and man and the extreme caution with which inferences drawn from animal experiments should be extended to man.

Hossmann & Zimmermann's work (78, 241) provides a further demonstration

of the protection afforded by pentobarbitone pre-treatment: brain damage was reversible in pre-treated monkeys subjected to 60 min of complete, global ischaemia produced by innominate and subclavian artery ligation.

Biochemical evidence for the protective action of barbiturates in brain ischaemia is less clear. Further, changes in high energy phosphate levels have been observed not to correlate with neurological dysfunction (51). Michenfelder and Milde (130), however, found less adenosine triphosphate (ATP) and phosphocreatine (PCr) depletion and lactate accumulation following MCA occlusion in squirrel monkeys anaesthetised with pentobarbitone than in control animals anaesthetised with halothane. Michenfelder & Theye (135) obtained similar results in dogs pretreated with thiopentone and subjected to acute haemorrhagic shock but only while the EEG remained active and not after it had become isoelectric. Nilsson et al. (151) found a lower rate of PCr and ATP depletion and lactate accumulation following cold injury in rats pretreated with phenobarbitone. Nordström et al. (152), on the other hand, found evidence of improved energy restitution in the brains of rats pretreated with phenobarbitone following 90 min of cerebral ischaemia without an improved energy status during the ischaemic episode itself.

In man, the evidence for the beneficial effect of barbiturates in cerebral ischaemia is even less convincing. They are commonly used for the control of seizures and have been used for some time for the control of intracranial hypertension (188) and prevention of its deleterious sequelae in head injury patients (192, 117, 38) and in Reye's syndrome (115) (post infectious encephalopathy of unknown etiology and pathogenesis associated with severe cerebral oedema, acute liver failure and systemic metabolic abnormalities). The mortality in Reye's syndrome was reduced from over 75% with standard treatment to zero with pentobarbitone therapy. In head injury patients with a baseline intracranial pressure of over 40 mmHg which could not be controlled by other means, a loading dose of 3-5 mg/kg pentobarbitone was effective in reducing the pressure in 76% of cases. Some of the patients had bilateral fixed, dilated pupils and were decerebrate before barbiturate therapy was started. Head injury patients with intracranial pressures in this range have previously been reported to have a mortality of 100% if the intracranial pressure cannot be controlled (137). In Marshall's series where pentobarbitone was given, 10 out of 19 of these patients recovered and returned to their former occupations.

Thiopentone is being given to patients after cardiac arrest in a trial using a standard dose regime of up to 30 mg/kg as soon as possible after restoration of the circulation (Pittsburgh Trials) (36). So far, there have been encouraging results in patients who had arrest times of between 5 and 22 min: 14 of 22 patients treated with thiopentone made a complete recovery, although this was sometimes delayed for as long as 18 days.

Mechanism of action of barbiturates

Steen & Michenfelder (201) have shown that the protective action of barbiturates is associated with their anaesthetic action. They used the optical isomers of methylphenobarbitone and found that the D isomer, which is inactive as an anaesthetic agent, did not protect mice in 5% oxygen, whereas the L isomer was effective in both respects. Further, this observation does not support the suggestion that free radical scavenging by barbiturates makes a significant contribution to their protective effect since both isomers might be expected to be equally active in this respect.

The metabolic depression induced by barbiturates is initially dose related. Michenfelder has shown, however, that increasing doses of barbiturates continue to depress the $CMRO_2$ only until the EEG becomes isoelectric. Further increasing the dose of barbiturate does not then further depress the $CMRO_2$. Similarly, no barbiturate protection of ischaemic brain was demonstrable in biochemical terms after the EEG became isoelectric (128, 135). He concluded that barbiturates primarily depress neuronal function; that this is possible only in tissue which is functioning and that depression of neuronal metabolism, $CMRO_2$ and CBF is secondary to functional depression. The reverse had previously been assumed, namely that barbiturates primarily depress neuronal metabolism and that loss of function follows secondarily. Michenfelder's conclusions, together with the assumption that metabolic depression is responsible for the protective action of barbiturates in cerebral ischaemia, are the basis for taking an isoelectric EEG as an end point for barbiturate therapy in practice. However, Crane et al. (47) have found that the major decrease in the cerebral metabolic rate for glucose (CMRG) in rat brain under the influence of pentobarbitone occurs with one fifth to one tenth of the usual anaesthetic dose. Subanaesthetic doses might therefore be expected to be effective for cerebral protection if this depends solely on metabolic depression. On the other hand, there is an apparent discrepancy in the doses which produce an isoelectric EEG in monkeys and the much higher doses which were needed to protect the brain against the effects of ischaemia. This had led to the suggestion of an independent 'membrane stabilising' action of barbiturates. The EEG in baboons becomes isoelectric when a dose of 50 mg/kg is

Table 4. Data from Hoff et al. (75) with permission of the American Heart Association, Inc.

No. baboons	Mean dose given (mg/kg)	Mean infarct size after 7 days, % cerebral hemisphere	Survival after 7 days
5	62	8·4	4/5
3	90	4·3	1/3
3	128	1·6	2/3
5	No pentobarbitone 1·1-1·26% halothane	14·9	4/4

exceeded. Although treatment with 62 mg/kg did reduce the mean infarct size following MCA occlusion to less than 10% compared with 15% in halothane anaesthetised control animals, treatment with 90 mg/kg resulted in significantly less infarction and 128 mg/kg in still smaller infarcts (mean about 3%) (75) (Table 4). One hundred and twenty mg/kg thiopentone also had a clear, though not complete, protective effect in rhesus monkeys in the Pittsburgh experiments referred to above (177) when given 60 min after a 16-min period of complete, global ischaemia accompanied by an isoelectric EEG. Yatsu's rabbits also had an isoelectric EEG before methohexitone was given.

These conflicting observations question the role of metabolic depression in barbiturate protection of the brain in ischaemia and thus the validity of using the EEG to titrate barbiturate dosage in clinical practice in order to obtain optimal results.

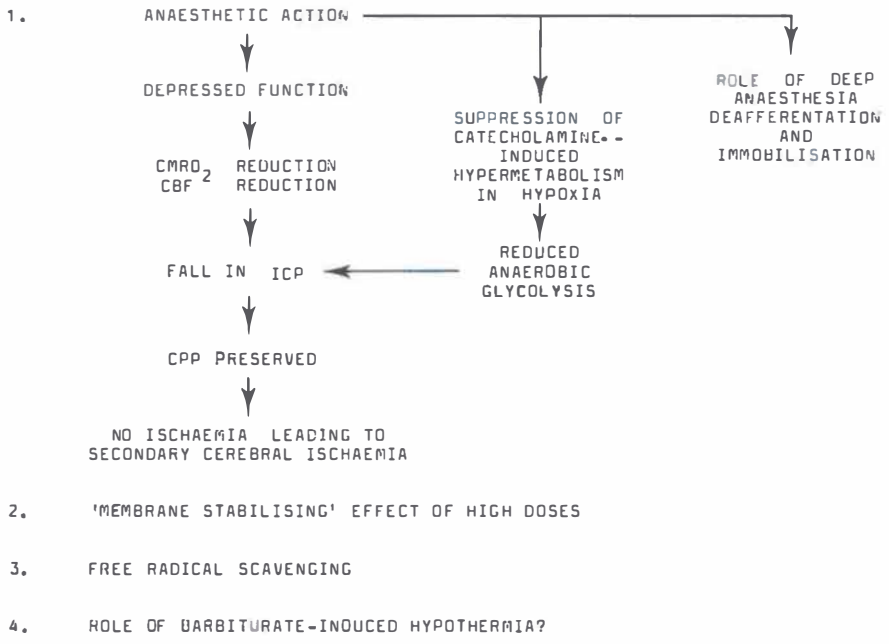

Fig. 1. Possible mechanisms of action of barbiturates.

The suppression of cyclic 3,5 AMP-mediated, catecholamine-induced hypermetabolism which occurs in hypoxia may play a central role in the protective action of barbiturates (146, 149) (Fig. 1). This could be their primary point of action which breaks the vicious cycles of events which follow an ischaemic episode and result in secondary damage (Fig. 2). Catecholamines stimulate glycolysis resulting in a greatly increased production of osmotically active

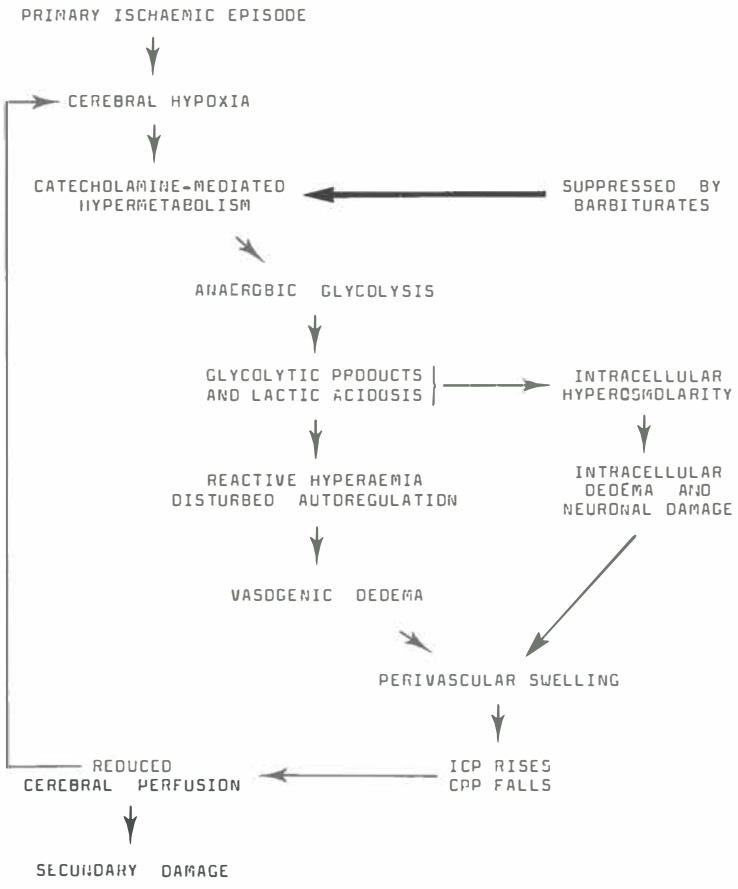

Fig. 2. Prevention by barbiturates of vicious cycles resulting in secondary and irreversible brain damage within 1-2 h.

intermediates, including lactate. Intracellular hyperosmolarity leads to cellular swelling which not only damages the cell but also produces capillary compression which further reduces cerebral perfusion. Barbiturates limit this sequence of events; cerebral vasoconstriction secondary to a depressed $CMRO_2$ also reduces the formation of vasogenic oedema which accompanies reactive hyperaemia and acidosis and contributes to pericapillary swelling. Both these sequences raise the intracranial pressure (ICP), reduce the cerebral perfusion pressure (CPP), jeopardise collateral perfusion and contribute to 'no-reflow' so that tissue hypoxia is continued and exacerbated.

Since barbiturates interfere with temperature regulation, a degree of accidental hypothermia may have contributed to the beneficial effects of barbiturate therapy in some reported cases. Hypothermia is well known to

protect the brain from the effects of cerebral ischaemia (163, 106, 123) and experimental brain injury (175). It use in neurosurgery has much declined since the 1960's (120) when moderate hypothermia was widely used in order to allow ligation or clipping of a cerebral aneurysm under conditions of partial or complete temporary cerebral circulatory arrest. At 28°C cerebral metabolic rate and oxygen consumption are about 50% of that at normal temperatures and 8-9 min of total circulatory arrest are considered to be safe.

Some good results have been obtained when hypothermia was induced in patients after cardiac arrest; some of these had severe neurological deficits following resuscitation (166, 24, 48). The rationale presented by these authors twenty years ago for the use of hypothermia following a period of cerebral ischaemia is much the same as that presented currently and outlined above for the use of barbiturates; that is the prevention of the development of cerebral oedema and secondary brain damage. The importance of cooling a patient promptly after such an episode is also emphasised.

Barbiturates and hypothermia appear to depress cerebral metabolism by different mechanisms and their effects are synergistic. Lafferty et al. (96) reduced $CMRO_2$ by 30% from control values in anaesthetised dogs either by cooling to 30°C or with 40 mg/kg pentobarbitone. In each case an active EEG was preserved. When the two were combined the $CMRO_2$ and CMRG fell by 70%. This could otherwise be achieved by cooling to 22°C. However, these observations are complicated by the fact that anaesthesia was induced in control and test dogs alike with 40 mg/kg pentobarbitone 4 h previously so that not only was there some cerebral metabolic depression in control animals but also some acute tolerance to barbiturate would have been present when the second dose was give to test dogs. Hägerdal et al. (66) reported a similar, synergistic effect on $CMRO_2$ and CBF in rats. As judged by biochemical criteria when the rats were subjected to hypoxia, hypothermia provided better protection than a dose of phenobarbitone which alone produced the same reduction of $CMRO_2$ and CBF. Nordström (153) also reported a synergistic effect on $CMRO_2$ and CBF in rats, using 150 mg/kg phenobarbitone and temperatures of 23°C and 27°C. Hypothermia alone induced after MCA occlusion was noted by Michenfelder & Milde (131) and Simeone et al. (187) not to mitigate the effects of the occlusion significantly in monkeys. In contrast, post-occlusion treatment with pentobarbitone alone, which was accompanied by a similar degree of metabolic depression, prevented the development of cerebral oedema during the first eleven hours after occlusion. Simeone et al. concluded from these results that cerebral protection by barbiturates is unlikely to be a direct result of metabolic depression *per se*.

Barbiturates and hypothermia have been used together clinically only occasionally, e.g. by Shapiro et al. (189) in head injury patients. The complexity of the clinical state makes it difficult to assess the value of such therapy.

Timing and dosage of barbiturate therapy

Some of the experimental evidence described above in which barbiturates have been shown to be effective in reducing brain damage when given some time after an ischaemic episode indicates that a substantial degree of damage occurs not at the time of insult but in the ensuing hours. Sundt et al. (208) found that in squirrel monkeys infarction developed not immediately following MCA ligation but over a matter of hours afterwards. Reactive hyperaemia followed restitution of flow and cerebral oedema associated with this was the chief cause of death in his animals, whether the occlusion was temporary or permanent.

Corkill et al. (44) demonstrated that 40 mg/kg pentobarbitone given to dogs 1 h after MCA occlusion reduced the mean infarct size from 21% of the hemisphere in animals anaesthetised with halothane to 5%, whereas the same dose given 2 h later was virtually without effect. He concluded that cerebral oedema results in impairment of the collateral circulation within 3 h. At this time little barbiturate could reach the ischaemic area and neuronal damage became irreversible. These considerations also suggest that barbiturate therapy should be most effective if given prophylactically before an episode of ischaemia. Molinari et al. (138) found

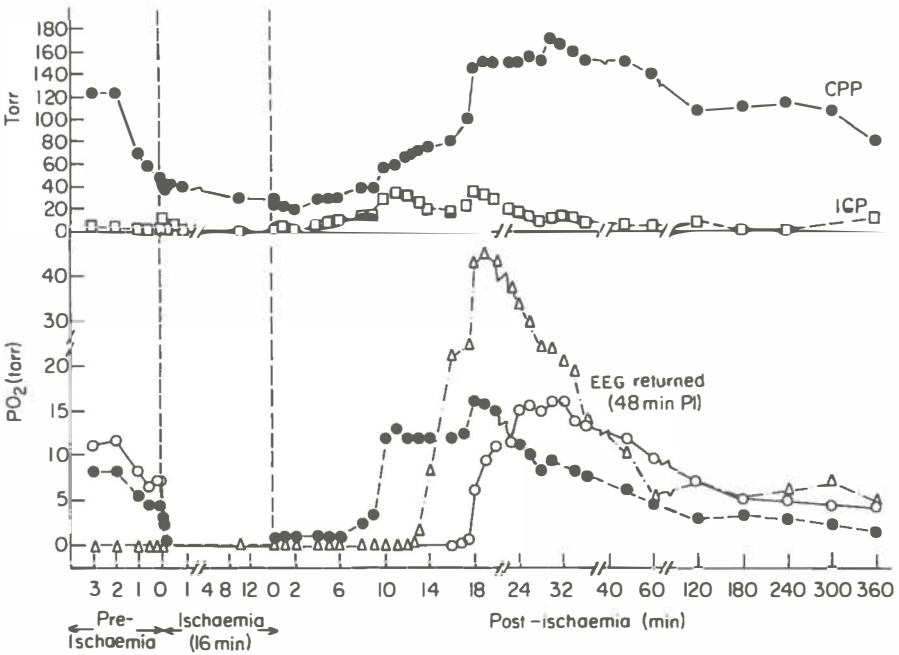

Fig. 3. Frontal cortex (FC), basal ganglia (BG) and occipital cortex (OC) tissue PO_2 after 16 min global brain ischaemia in the rhesus monkey. From Nemoto (181) with permission of the American Heart Association, Inc. Key to lower graph: △— · —△ BG; ● - - - ● FC; ○——○ OC.

that the regional cerebral blood flow (rCBF) in areas with collateral circulation in macaques pretreated with phenobarbitone recovered to control values within three hours following MCA embolisation, whereas in ketamine anaesthetised animals there was no recovery. Nemoto et al. (181) using the primate model of global brain ischaemia described above, found that following an initial hyperaemic phase, postischaemia the cortical tissue P_{O_2} dropped to below pre-ischaemic values within 60-120 min of reperfusion and remained low for up to 6 h (Fig. 3). This implies that continuing hypoxia is involved in the development of secondary ischaemic brain damage and emphasises the need for prompt treatment in order to avoid the development of pericapillary and neuronal oedema which limits reperfusion and impairs collateral flow with resulting secondary damage. The results of Safar's experiments imply that brain damage in the rhesus monkey after 16 min of complete, global ischaemia is potentially completely reversible or preventable. They also illustrate the possibility of overcoming a time delay in starting barbiturate therapy by using a larger dose of barbiturate: 120 mg/kg thiopentone given 60 min postischaemia produced a neurological deficit score of only 7% when assessed after seven days compared to 53% in control animals and 18% when 90 mg/kg was given with a delay of 15 min. It is not clear why 120 mg/kg given 30 min postischaemia did not result in comparable neurological recovery in these experiments.

Doses of barbiturate which have been used clinically vary widely and range from a loading dose of 30 mg/kg thiopentone (36) and of 3-5 mg/kg pentobarbitone with blood levels maintained at 2·5-5 mg/dl in head injury patients (117) to over 500 mg/kg thiopentone given over 48-72 h after cardiac arrest (172) or over 20 h postoperatively by the authors (18).

Blood levels of barbiturate alone cannot be used as a guide to effective dosage partly because the existence of acute tolerance means that a given blood level is not associated with a constant degree of cerebral metabolic depression except after single dose. Pretreating dogs with 10 mg/kg thiopentone, which itself caused a 9% depression in $CMRO_2$, reduced the depression of $CMRO_2$ produced by 23 mg/kg thiopentone given two hours later from 40% to 17% (7).

If maximal cerebral metabolic depression is associated with an isoelectric EEG, as discussed above, the EEG could be used to titrate barbiturate dosage on the assumption that cerebral protection is related to metabolic depression. Doses in this range, however, usually are associated with severe cardiovascular depression so that a burst-suppression EEG pattern may be a more satisfactory endpoint in clinical practice. This was used by Bruce (38) in the treatment of head injury patients. Haemodynamic considerations may further limit the dose of barbiturates which can be used safely after cardiac arrest, particularly in the presence of myocardial infarction.

Marshall & Shapiro (115, 117) used the ICP and CPP together with blood levels

of barbiturates as a guide to dosage without regard to the EEG and obtained good results in spite of the fact that barbiturate therapy was started only at a late stage after other measures had failed to control the ICP. There is thus conflicting evidence regarding the dose of barbiturates which is effective in protecting the brain from the effects of ischaemia under experimental conditions. Further, there are at present no established criteria for optimal dosage when using barbiturates for this purpose in clinical practice.

CHAPTER III.2

Barbiturate therapy in the management of cerebral ischaemia

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M. Belopavlovic and A. Buchthal

Summary

Two patients who underwent surgery for cerebral aneurysms are presented. In the first case 31 g thiopentone were given postoperatively over 20 h after the patient had already been comatose for many hours. Such high doses raise considerable problems in patient management. In the second case a loading dose of 50 mg/kg thiopentone was given prophylactically to a patient undergoing cerebral aneurysm surgery beginning at the induction of anaesthesia and before surface cooling was begun. Cerebral activity was monitored continuously with a cerebral function monitor (CFM). There was no significant cardiovascular depression, little delay in postoperative recovery and no permanent neurological sequelae.

In cerebral aneurysm surgery, cerebral oedema following cerebral ischaemia, either associated with vasospasm or resulting from surgical occlusion of vessels, remains a major problem postoperatively and may be an indication for preventive treatment with barbiturates. The authors contend that this technique merits further evaluation in cerebro-vascular surgery, especially in high risk cases.

The action of barbiturates in protecting the brain against the effects of cerebral ischaemia has been reviewed in another paper in this issue (17). There are now a number of clinical reports of their use in cerebral ischaemia resulting from cerebral oedema, cardiac arrest or local vascular insufficiency. In patients with head injuries or Reye's syndrome (38,115,116,117), barbiturates have been used only at a late stage after it was clear that their intracranial hypertension was uncontrollable by conventional means and the prognosis would otherwise be considered to be hopeless. The time interval from the injury or from the time at which the patient's condition began to deteriorate is often not described. The experimental work reviewed by the present authors (17), however, indicates that prompt action is crucial to the success of barbiturate therapy so that better results might be expected if this is initiated with minimum delay. Early treatment is attempted in the Pittsburg trials (189) in which thiopentone is given to patients

after cardiac arrest, if possible within 10 min of restoration of the circulation. Thiopentone has also been used intraoperatively for the rapid reduction of intracranial pressure (36). Planned procedures where patients are pretreated with barbiturates before a time of potential risk to the cerebral circulation such as during carotid artery and cerebrovascular surgery might be expected to yield the best results. However, in this case the results are very difficult to interpret as the risk to the patient cannot usually be assessed beforehand and subjects cannot be matched for a controlled trial.

Early initiation of barbiturate therapy after an episode of cerebral ischaemia not only calls for very precise definition of the indications for therapy but also presents a number of difficulties.

In patients who sustain head injuries it would appear that those who are conscious and rational immediately following the injury and begin to deteriorate later should be regarded as developing brain damage which is potentially reversible or preventable and should therefore be given barbiturates as soon as assessment on the Glasgow Coma Scale and neurological assessment indicate deterioration. This can be done regardless of the intracranial pressure or electroencephalogram (EEG) at that time provided that a diagnosis has been made and that other treatable causes of the deterioration, such as intracranial haemorrhage or cardiopulmonary problems have first been excluded. This involves a full neurological assessment, obtaining skull and chest X-rays, computerised tomography (CT) scanning and angiography. These procedures necessarily take a certain time. Further, there may be some delay before the patient reaches hospital and a reliable neurological assessment can be made. The patient's prognosis may be difficult to assess when barbiturate therapy is begun and this should be explained to the relatives. The anaesthetist, neurologist and neurosurgeon should undertake such therapy in cooperation and every attempt should be made to avoid starting barbiturate therapy in patients who may be considered to have sustained irreversible brain damage.

Neurological assessment becomes very difficult in a comatose patient requiring artificial ventilation and receiving barbiturate therapy. Tendon reflexes, brainstem evoked responses and evoked potentials may persist while pupil signs, corneal reflexes and caloric responses disappear under the influence of large doses of barbiturates.

The intracranial pressure should be monitored continuously. If it is high initially a good response to barbiturates favours a good prognosis (116). EEG's and CT scans should be made intermittently; a continuous record of cerebral activity can be obtained with a cerebral function monitor (CFM)(Devices).

The electrocardiogram (ECG), arterial blood pressure via an arterial line, central venous pressure and end tidal CO_2 concentration should be routinely monitored, as should blood biochemistry. In some patients the use of a Swan

Ganz catheter for the measurement of pulmonary artery wedge pressure and cardiac output by thermodilution may be indicated. Blood barbiturate levels should be estimated regularly and the maintenance of levels higher than the usual 2·5-3·5 mg/decilitre pentobarbitone should be considered if there has been a substantial delay before therapy was started. Discontinuing barbiturate administration in order to make a neurological assessment may be detrimental and predisposes to the development of tolerance if barbiturate therapy is resumed later. The result may be reduced efficacy of the same dose of barbiturates, or, if the dose is increased to maintain the same degree of cerebral depression, troublesome cardiovascular depression. The patient should be in a stable haemodynamic state before barbiturates are given. Cardiovascular depression may limit the dose and rate of administration of barbiturates which can safely be given, particularly to patients with cardiac disease. These patients may also be more prone than others to dysrhythmias so that the use of cardiotonic drugs may also be limited. Isoprenaline or dopamine or both may be needed to maintain cardiac output and peripheral perfusion. Urine output should be maintained at least at 60 ml/h.

Patients receiving barbiturate therapy also face all the problems associated with prolonged intubation, ventilation and immobility together with depressed responses, including the cough reflex. Frequent physiotherapy must therefore be given with efficient postural drainage and suction and the patient should be turned regularly in order to avoid atelectasis and hypostatic pneumonia as well as skin damage and venous thrombosis. The eyes should be covered to prevent corneal damage. These patients are very susceptible to infection since all body defences are depressed, particularly if they are also receiving steroids in high doses, so that antibiotics may be given prophylactically. Low dose heparin therapy may also be given in order to prevent thrombotic complications.

Blood barbiturate levels may take a considerable time to fall after the administration of high doses is discontinued and recovery may be much delayed.

Case 1

The patient, a female aged 51 years, was admitted 25 days after a subarachnoid haemorrhage. This had been accompanied by headache and vomiting without loss of consciousness and was followed by labile hypertension. She had a history of repeated bronchitis and of mild hypertension for some years which had been treated with a diuretic. On admission there was no neurological deficit; the arterial pressure was 135/90 mmHg and the cerebrospinal fluid (CSF) was clear. Four vessel angiography showed a saccular aneurysm of the anterior communicating artery, three anterior cerebral arteries and an absent left vertebral artery.

Surgery was carried out under steroid cover. Seldinger angiography was repeated 45 minutes after premedication with atropine, promethazine, chlorpromazine and pethidine.

Endotracheal anaesthesia was induced with pancuronium, thiopentone, suxamethonium and pethidine and continued with pancuronium, pethidine, droperidol and ventilation with 33% O_2, 67% N_2O. After placing three large peripheral intravenous lines, an oesophageal stethoscope and oesophageal, rectal and skin temperature probes, the patient was moved to a water bath. The water bath is used as an operating table as well as for cooling and rewarming the patient. The patient was cooled to an oesophageal temperature of 32·5°C with iced water at 10°C. Water was then drained from the bath and lumbar puncture performed through a hatch. Arterial pressure was monitored via the Seldinger catheter and end-tidal CO_2 with a capnograph (Godart).

A right frontal craniotomy was undertaken; 120 ml CSF were drained to facilitate surgery after the dura was opened. The aneurysm was then localised by further angiography. Anaesthesia proceeded uneventfully. A sodium nitroprusside infusion was started at 80 μg/min as the arterial pressure rose to 160/100 mmHg with surgical retraction and the mean arterial pressure (MAP) was allowed to fall to 65 mmHg during dissection of the aneurysm.

The aneurysm was effectively excluded from the cerebral circulation with a clip but this proved possible only at the expense of obliterating one of the three anterior cerebral arteries. The nitroprusside infusion was then discontinued, the arterial pressure rose to 120/70 mmHg and rewarming was begun. Epidural transducers (Philips) were placed symmetrically in frontal burr closure. At 18.15 hours the oesophageal temperature reached 35·7°C, the patient opened her eyes and was able to obey commands; she was extubated and transferred to the Intensive Therapy Unit. The pupils were equal and reactive but she was aphasic and had a right hemiparesis. The epidural pressures immediately postoperatively were 4·5 mmHg on the right and 1·1 mmHg on the left. The dexamethasone was continued and usual anticonvulsant doses of phenobarbitone and phenytoin given.

The patient's level of consciousness deteriorated during the night and the following morning she was comatose, unresponsive to painful stimuli and had a right hemiplegia. The pupils were equal and reactive. During the course of the day the epidural pressures rose to 33 mmHg on the right, 16 mmHg on the left. The patient became unresponsive and areflexic. At 19.00 hours she was taken back the theatre for re-exploration. A small extradural haematoma was found with global cerebral oedema. The bone flap of the craniotomy was removed and only the left epidural transducer was left in place.

Postoperatively, the patient was left intubated and ventilated and remained unresponsive and areflexic. The pupils were pinpoint, unequal, the right larger

than the left, and unreactive. The left epidural pressure was 12 mmHg initially and rose to 15 mmHg. She was started on ampicillin and cimetidine. At this time it appeared that nothing more could be achieved with conventional therapy and barbiturate therapy was started at 23.00 hours in agreement with the neurosurgeons; 1·5 grams of thiopentone were given slowly intravenously followed by an infusion of 2·5 g/h (about 50 mg/kg/h). Neither EEG nor CFM control was available at this time. A dopamine infusion was required to maintain the MAP above 80 mmHg (a cerebral perfusion pressure of 70 mmHg for the left side as the left epidural pressure fell to 10 mmHg). Arterial and right atrial pressures were measured directly together with left epidural pressure and end-tidal CO_2 concentration which was maintained at 3·7-4·5%. The patient received 500 ml 5% human albumin and 6 mEq/h KCl and remained warm with a good urine output overnight.

Two days postoperatively the EEG was isoelectric and the pupils remained fixed, the right larger than the left. Cerebral activity was monitored continuously with a CFM (Devices). The thiopentone infusion was discontinued at 19.30 hours after a total dose of over 31 g had been given over 20 h. The highest measured serum thiopentone level was 166 mg/litre. The serum thiopentone levels are shown in Fig. 1. Ventilation was continued with 40% O_2 in air. Diuresis continued at over 150 ml/h and the plasma K^+ remained at 2·8 mmol/litre despite the administration of 4·8 mmol/h. Plasma Na^+ rose to 164 mmol/litre and osmolality to 314 milliosmoles/litre.

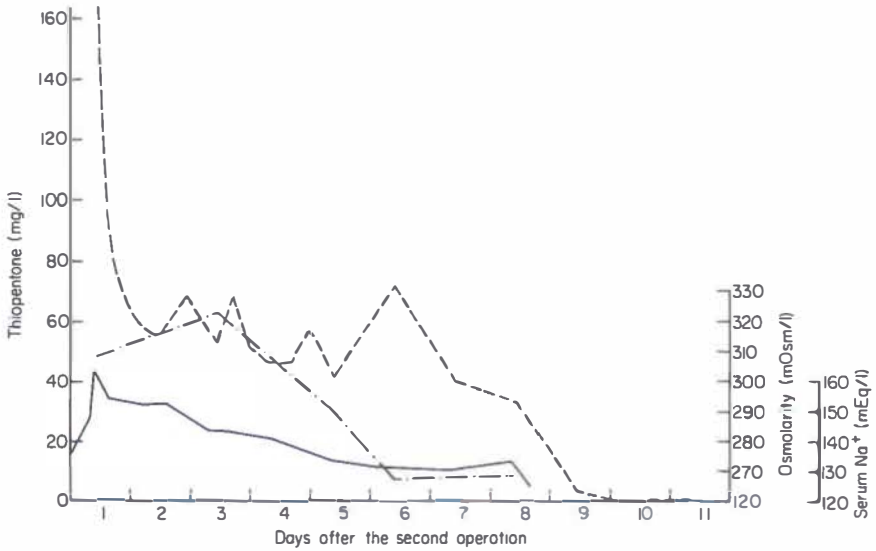

Fig. 1. Case 1. Serum thiopentone levels, serum osmolalities and sodium concentrations: 1-12 days after the second operation. – – – – Serum thiopentone levels (mg/l); ——— Serum Na^+ (mEq/l); — · — · — Serum osmolality (mOsm/l).

On the fourth postoperative day the serum thiopentone level had fallen to 56 mg/litre while the EEG showed a burst-suppression pattern with much longer periods of suppression than of bursts. The neurological progress of the patient is shown in Fig. 2. On the sixth postoperative day the pupils were equal and reactive, there was a positive response to caloric testing; corneal, lash and tendon reflexes were present and the patient was coughing on tracheal suction. The CFM trace was now much narrower and the baseline about 8 μV. She developed a left lower lobe hypostatic pneumonia which required continued ventilation with +5 cm H_2O end-expiratory pressure, physiotherapy and gentamicin.

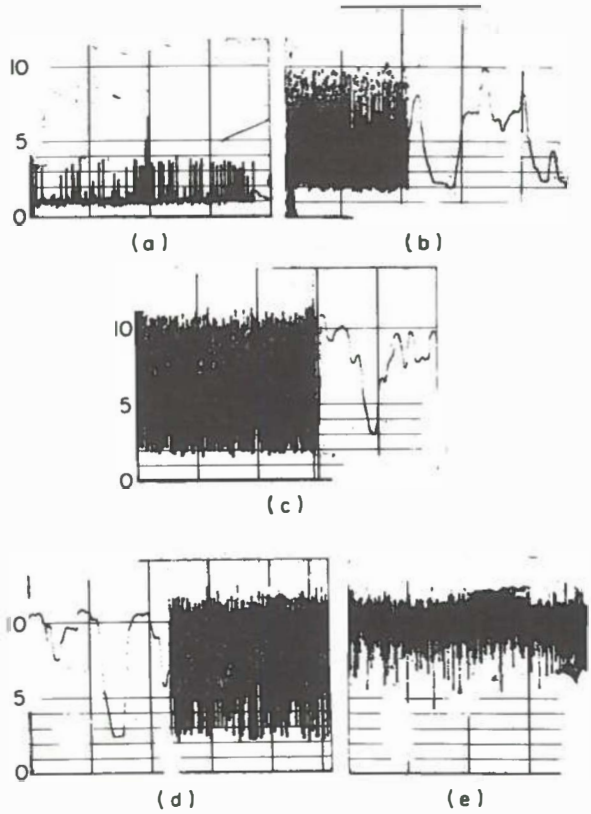

Fig. 2. Case 1. Cerebral Function Monitor (CFM) record: 1-5 days after the second operation.
a) First day: 1730 hours. Thiopentone level 73 mg/l. Pupils pinpoint, unreactive and unequal (right>left). Patient areflexic and unresponsive. EEG iso-electric.
b) Second day: 0730 hours. Thiopentone 56 mg/l. Pupils unreactive but equal. EEG showed burst-suppression.
c) Third day: 2000 hours. Thiopentone 68 mg/l. Pupils intermittently reactive and unequal (right>left). No response to caloric testing.
d) Fourth day: 1000 hours. Thiopentone 54 mg/l. Pupils reactive and equal.
e) Fifth day: 1500 hours. Thiopentone 47 mg/l. Eyelash, corneal and tendon reflexes present, coughing on tracheal suction.

Nine days after starting thiopentone therapy the patient obeyed commands and appeared to be fully aware; the blood thiopentone level was now zero. She was extubated 14 days after barbiturate therapy was started; she appeared to be aphasic and had a right hemiplegia. A CT scan showed evidence of a left frontal infarct (Fig. 3). She began to talk after a few days and the power in her right arm and leg improved.

She was discharged home within 3 months postoperatively and has a mild, residual hemiparesis which continues to improve.

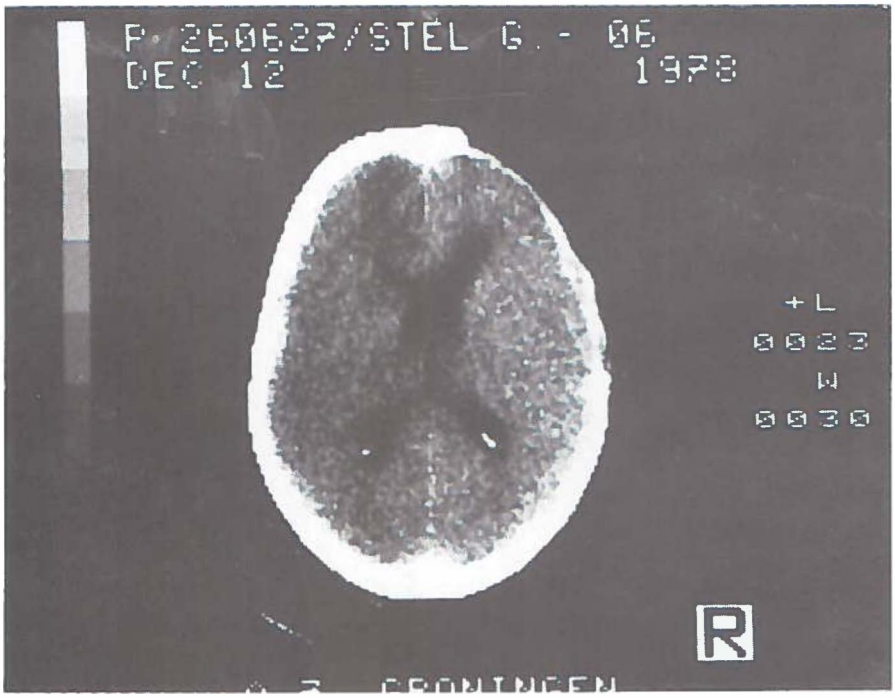

Fig. 3. Computerised tomography (CT) scan twenty days after the second operation showing a left frontal infarct.

Discussion

A massive dose of thiopentone was given to this patient after her condition failed to improve following surgical decompression and conventional management. She had been deeply comatose for more than 15 h and the pupils had been unreactive for more than 8 h before barbiturates were given. A large dose was given in order to keep the EEG isoelectric for at least 24 h; however no EEG or CFM control was available at that time and it was considered unacceptable to delay barbiturate therapy further for this reason. The difficulties

of neurological assessment during high dose barbiturate therapy and controlled ventilation have been mentioned; such assessment can therefore be of no assistance in titrating the dose of barbiturates or the patient's response to therapy.

The large dose which was given (over 31 g thiopentone during 20 h) may have contributed to the good recovery made by this patient with relatively little residual disability despite her poor initial condition and the long delay before therapy was started. This suggests that the consequence of a long delay might have been partly overcome by using such high doses. The case also indicates the lack of any specific 'toxic' effects of high doses of barbiturates. However, cardiovascular depression can be troublesome and careful maintenance of cardiac output, cerebral perfusion pressure, urine output and peripheral perfusion using cardiotonic drugs was required.

Such patients are completely immobile with little muscle tone and require meticulous attention; this patient developed a hypostatic pneumonia despite our efforts regarding ventilation and physiotherapy, which further delayed her recovery.

The plasma potassium concentration was persistently low during the first day of barbiturate therapy; the plasma osmolality and sodium were high for a few days (Fig. 1). The reason for these changes is not clear; less than 160 mmol sodium were given as thiopentone.

The large difference between the intracranial pressures measured by the epidural transducers on the two sides before barbiturates were given is striking, as was the apparent ineffectiveness of removing the bone flap on the right in decompressing the left hemisphere, where the pressure not only failed to fall but continued to rise to over 20 mmHg during the next 5 days. The left epidural pressure fell initially when thiopentone was given; the later rise may be related to the development of the left frontal infarct, or to a recurrence of global cerebral oedema associated with tolerance to barbiturates and falling blood thiopentone levels as well as to the return of muscle tone and straining against the ventilator.

The development of transient aphasia with a persistent hemiplegia on the side of the operation is perhaps remarkable; it is not accounted for by occlusion of the anterior cerebral artery which was known to have occurred during surgery. It may, however, be explained by occlusion or vasospasm associated with thrombosis of the left recurrent artery of Heubner. This vessel, usually arising from the anterior cerebral artery, has branches supplying the anterior limb of the internal capsule as well as parts of the basal ganglia, anterior hypothalamus, uncinate fasciculus and olfactory regions. Its occlusion is known to result in hemiparesis with severe weakness of the arm, mild weakness of the face, tongue and palate and aphasia if the artery is on the dominant side (157). The origin and anatomy of the artery and its branches are known to be variable; they may arise from the internal carotid bifurcation, middle cerebral artery or anterior

communicating artery. They are seldom seen on angiography or during surgery especially without the use of a microscope and are therefore very vulnerable to the effects of manipulation during dissection of an aneurysm.

Case 2

The patient, a female aged 40 years, had a subarachnoid haemorrhage with sudden onset of headache and vomiting but with no loss of consciousness. On admission to the Neurosurgical Unit the same day there was no neurological deficit or neck stiffness; there were no other relevant findings. She had previously been well except for mild hypertension in the last 2 yr which had been treated only with a low salt diet.

Seldinger angiography revealed a midline aneurysm of the anterior communicating artery and evidence of marked vasospasm in the first part of the right middle cerebral artery, the last part of the right internal carotid artery and in the right anterior cerebral artery. She was prepared for operation 19 days after admission. Pre-operative angiography the same morning again showed marked vasospasm of vessels on the right side and was followed by aphasia and a right hemiparesis which resolved completely within 6 h. Surgery was postponed and performed 16 days later without further angiography.

The patient was premedicated with atropine, pethidine, promethazine and chlorpromazine. Anaesthesia was induced with an infusion containing 3 g thiopentone (50 mg/kg). Suxamethonium was used to facilitate intubation and anaesthesia was continued with pethidine 200 mg, pancuronium and ventilation with 33% O_2, 67% N_2O. The 3 g thiopentone infusion was given over 40 min and was completed before cooling was begun. Anaesthetic management was otherwise similar to that described in Case 1. Cerebral activity was recorded peroperatively with a CFM.

A right frontal craniotomy was performed and 120 ml CSF were drained after the dura was opened. The mean arterial pressure did not drop below 75 mmHg (90 mmHg systolic) at any time and cardiotonic drugs were not required. No hypotensive drugs were given. The serum thiopentone level after the end of the infusion was 55 mg/litre. During dissection of the aneurysm the oesophageal temperature was 28·3°C, the serum thiopentone level was between 18 and 24 mg/litre, the lumbar CSF thiopentone level was about 2 mg/litre and the CFM baseline was 2 microV.

The aneurysm involved the origins of both anterior cerebral arteries as well as two other arteries supplying the hypothalamus and midbrain so that it would have been impossible to exclude it from the circulation without permanently occluding one or more of these. The aneurysm was therefore wrapped in a piece of temporal muscle and no attempt was made to clip its neck. The patient was rewarmed.

During closure an epidural transducer was placed in one of the burr holes; it recorded 3 mmHg immediately postoperatively. The patient was left intubated, transferred to the Intensive Therapy Unit with a temperature of 36°C and was ventilated for 6 h. After this time she was fully awake with no apparent neurological deficit and was extubated; the serum thiopentone level was 7 mg/litre. Recovery was uneventful except for the development of a partial right third nerve palsy and ptosis 2 days postoperatively. These resolved over the following few weeks.

Discussion

The development of a hemiplegia and aphasia following angiography in this patient suggested that she would be especially vulnerable to the effects of vasospasm associated with manipulation during surgery. For this reason it was decided to give her a loading dose of 50 mg/kg thiopentone prophylactically since pretreatment might be expected to yield better results than giving barbiturates after the cerebral circulation has already been compromised. In addition, loading a patient at induction avoids the necessity of giving large doses of intravenous barbiturates while the patient is hypothermic, when troublesome cardiovascular depression might be anticipated. The case illustrates the feasibility of giving this dose of thiopentone together with hypothermia, in this case resulting in a serum level of about 20 mg/litre thiopentone at 28·3°C. Experimental work suggests (66,96) that such a combination may be more effective than the use of either alone in protecting the brain against ischaemic damage.

A loading dose of 50 mg/kg seems to be satisfactory as there was no significant cardiovascular depression or delay in postoperative recovery while the CFM baseline was adequately depressed to 2 microV, corresponding to a burst-suppression EEG (Fig. 3, Case 1). Less narcotic is necessary when a loading dose of barbiturate is given.

The development of a transient, partial third nerve palsy and ptosis 2 days postoperatively is perhaps remarkable and raises the question of whether these might have been apparent immediately postoperatively and been more persistent in the absence of barbiturate therapy.

The authors suggest that the procedure used in this case merits further evaluation for routine use in cerebral aneurysm surgery where the precise operative procedure and its consequences and thus the risk to the patient cannot always be assessed preoperatively.

CHAPTER III.3

Barbiturates for cerebral aneurysm surgery

A review of preliminary results

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M. Belopavlovic, A. Buchthal and J. W. F. Beks

Summary

Ninety-two cerebral aneurysm cases treated by clipping under moderate hypothermia are reviewed. Twenty-three of these cases received pentobarbitone during surgery in doses sufficient to render the EEG flat. The overall combined mortality and morbidity (complication rate) among 69 non-barbiturate cases was 21.7%. There were significant differences in results between aneurysms in different anatomical locations. The complication rate among eight middle cerebral artery aneurysm cases was 62.5% and among ten internal carotid artery bifurcation cases 40%, while that among nineteen internal carotid artery cases was 16% and among 27 anterior communicating complex cases 7.4%. The overall complication rate among 23 pentobarbitone cases was 17%. There were no complications among eight middle cerebral artery cases; one of two internal carotid bifurcation cases became hemiplegic following occlusion of the middle cerebral artery at its origin. The complication rate among nine internal carotid cases was 22%. No difficulties were experienced regarding haemodynamic stability or cardiac rhythm while using pentobarbitone at normothermia or at 28°C. It is suggested that cerebral aneurysms involving the middle cerebral artery which appear to be most at risk may have the most to gain by the prophylactic use of pentobarbitone during surgery.

Introduction

Cerebral vasospasm and the potentially catastrophic consequences of cerebral ischaemia and oedema which may ensue remain a real threat to the cerebral aneurysm patient and to the neurosurgeon today. Barbiturates have been shown to be effective in primate stroke models both in reducing the extent of cerebral infarction observed histologically (25, 75, 144, 239) and in ameliorating the neurological sequelae to permanent arterial occlusion (130, 132, 193) as well as in focal ischaemia of limited duration (184). It is much less clear at the present time how much protection barbiturates can offer in global ischaemia, simulating the cardiac arrest situation (27, 59, 195, 204, 226).

Much of the published clinical trials of barbiturates to date are concerned with the control of intractable intracranial hypertension in head injuries (117, 170, 189) metabolic encephalopathy (115, 230) or in cerebral oedema of other aetiologies (236) rather than with brain protection in acute, focal cerebral ischaemia. The difficulty of assessing the results of barbiturate therapy in the case of head injury patients is increased further by the inevitably wide variation in several important factors. These include the site, nature and extent of the brain injury; the time interval from the injury to the institution of therapy, which may be too long to allow maximum benefit from barbiturates (26, 44, 185), the adequacy of respiratory and haemodynamic support during this interval and the extent of development of secondary changes in that time.

Planned cerebral aneurysm surgery offers a much more controlled situation for the assessment of the efficacy of barbiturates in combating the effects of cerebral ischaemia, although cases still vary in some respects and the ischaemic risk to each cannot usually be precisely estimated. Nevertheless, the patient's clinical and neurological state immediately prior to surgery is accurately known; the nature of the pathology and of the intervention are precisely known with the aid of peroperative angiography and it is possible to administer barbiturates without delay when required.

Although barbiturates may be effective when given within a limited time after the onset of an ischaemic insult (26, 44, 185) we have chosen to load the patients prophylactically and to discontinue administration when the period of greatest hazard is estimated to be over. In the event of complications such as permanent vascular occlusion or severe, persistent segmental vasospasm the administration of barbiturates can be continued into the postoperative period without interruption. Our experience so far with this technique has enabled us to reappraise the indications for the use of barbiturates in high doses in cerebral aneurysm surgery.

Patients and Methods

During the period 1974 to 1983 one hundred and twenty cerebral aneurysm cases were treated operatively in the Neurosurgical Department of the University Hospital in Groningen. In the latter four years twenty-eight cases were given prophylactic pentobarbitone in high doses during surgery. The first 50 non-barbiturate cases were consecutive and were studied retrospectively from existing records. Barbiturates were initially used after two cases at this time developed serious complications. Six patients who received thiopentone sodium are not presented here since this technique is no longer used (19). The first 19 pentobarbitone cases were consecutive; the next six were elected according to availability of staff and facilities and the estimated risk to the patient of the additional postoperative period of immobility, rather than according to the

preoperative Hunt and Hess grade (84) or the anatomical location of the aneurysm. The last three pentobarbitone cases were selected according to our findings reported here, *i.e.*, according to the anatomical location of the aneurysm.

All aneurysms had ruptured at least once prior to surgery. Surgery was carried out as soon after admission as the patients' neurological condition was stable but was usually postponed in the presence of marked cerebral vasospasm. Cerebral angiography (Seldinger technique) was performed immediately before surgery in nearly all cases, under local anaesthesia whenever possible, to assess the state of the vessels; the catheter was left in place for peroperative angiography to allow confirmation of the position of the clip and the patency of vessels and to assess the severity and extent of vasospasm after clipping, if present. Surgery was performed by one operator (JWFB) in all except five nonbarbiturate cases and in all but four pentobarbitone cases (three clipped cases). A frontal approach was used with magnification. Self-retaining retraction was not employed. In all cases except one, surgery was performed under moderate hypothermia at 27 to 29°C. This was induced by surface cooling with cold water following premedication with a lytic cocktail (pethidine, 50 mg; promethazine, 25 mg; chlorpromazine, 25-50 mg and atropine, 0.5 mg, intramuscularly). The waterbath serves as an operating table with a 15° head up tilt. Surgical access was further improved by the lumbar drainage of up to 120 ml of cerebrospinal fluid via a hatch in the waterbath after the dura was open.

All patients received dexamethasone, 16 mg daily, starting 24 hours preoperatively. The dose was reduced from the third postoperative day in non-barbiturate cases and the fifth postoperative day in pentobarbitone cases.

Anaesthesia

Anaesthesia was given or supervised by one of the authors (M.B.) in all except one non-barbiturate case. Anaesthesia was induced with thiopentone sodium in all non-barbiturate cases. Etomidate was used in the pentobarbitone cases in order to minimize the development of tolerance as far as possible before giving pentobarbitone (7, 202). Intubation was carried out with the aid of suxamethonium chloride and anaesthesia was continued with pethidine, pancuronium and ventilation with 33% oxygen, 65% nitrous oxide and 2% carbon dioxide to maintain the arterial carbon dioxide tension at 4 to 5 kP at the prevailing body temperature. Sodium nitroprusside was used when necessary to control the arterial blood pressure and to reduce it to a mean of 50 to 70 mmHg during dissection of the aneurysm. Inspired gases were humidified at 38°C in all the pentobarbitone cases and in the last 30 non-barbiturate cases. All patients were rewarmed to 36.5°C at the end of the surgery. Non-barbiturate cases were

generally awake at the end of surgery and were extubated in the absence of complications. Frontal epidural pressure was monitored postoperatively in the first 52 non-barbiturate cases and in all the pentobarbitone cases.

The patient and relatives were informed in advance when pentobarbitone was used. A bolus of 600 mg was given during cooling and a 1% infusion at 5 to 10 mg/minute started at the same time. Cerebral activity was monitored using a Cerebral Function Monitor (CFM) (Devices) (119). A signal obtained from biparietal scalp electodes is subjected to heavy filtering and logarithmic amplitude compression, retaining only frequencies between 2 and 15 Hz. It is displayed as a single trace and can be recorded continuously on a chart recorder for long periods of time. A typical CFM trace during loading with pentobarbitone is shown in Fig. 1. The rate of pentobarbitone infusion is adjusted to keep the CFM trace flat until the clip has been placed and checked by angiography. Pentobarbitone is then discontinued. The total amount of pentobarbitone given is therefore related to the duration of the procedure.

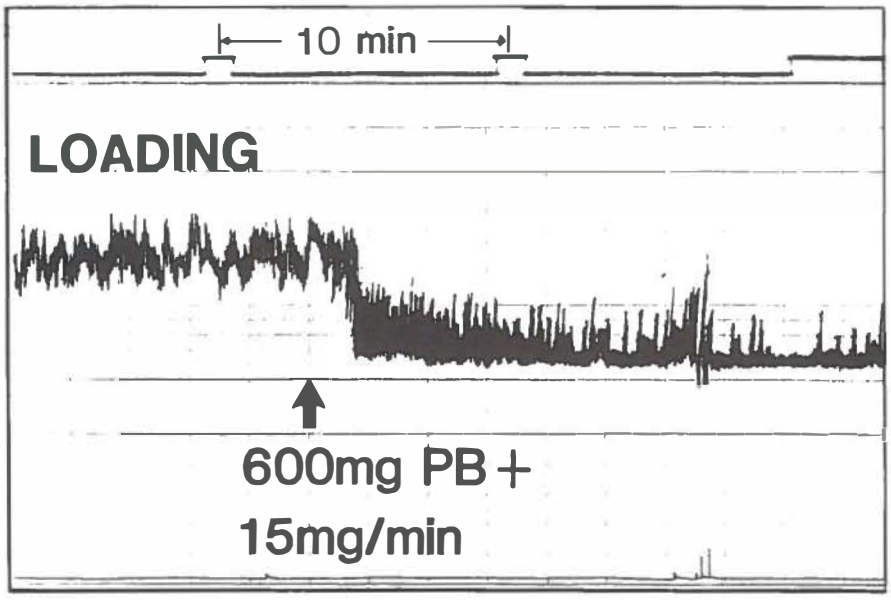

Fig. 1. Cerebral Function Monitor recording during loading with pentobarbitone.

Postoperatively, patients who had received pentobarbitone were ventilated for as long as necessary. They were extubated after a mean of 37 hours postoperatively. Postoperative monitoring included epidural intracranial pressure, CFM, end-tidal CO_2 and intermittent arterial blood gas, acid-base and electrolyte estimation.

Intraoperative monitoring included: EKG; arterial blood pressure via a radial cannula (Statham transducers); end-tidal CO_2 (Godart Mark II capnograph); oesophageal, nasopharyngeal and skin temperatures (Ellab); right atrial pressure; CFM; intermittent arterial blood gas, acid-base and electrolyte estimation and urine production.

Non-barbiturate patients received phenytoin sodium, 300-500 mg, during rewarming. Pentobarbitone cases were started on phenytoin, 300 mg daily, 24-36 hours postoperatively.

Sodium pentobarbitone was obtained from the Hospital Pharmacy. Pentobarbitone levels were estimated using high performance liquid chromatography.

Focal neurological deficits only are reported in this study.

Results

1. Haemodynamic aspects

Systemic arterial blood pressure and the incidence of cardiac dysrhythmias were similar when using pentobarbitone to those seen in non-barbiturate cases at comparable temperatures. Hypotension was never seen. Sodium nitroprusside was frequently required during the administration of pentobarbitone to control the arterial blood pressure during dissection of the aneurysm, particularly in the presence of cerebral vasospasm.

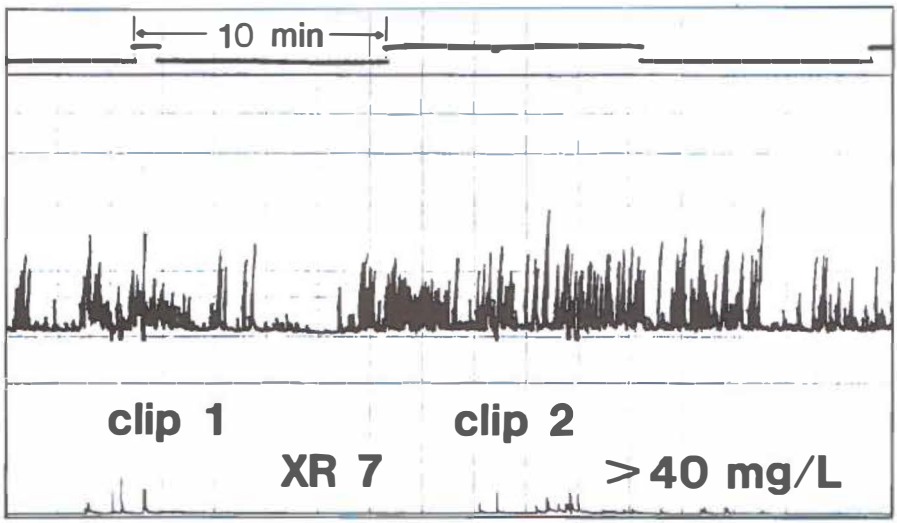

Fig. 2. Cerebral Function Monitor recording during dissection of aneurysm. Pentobarbitone infusion 5 mg/min; patient temperature 29-29°C. Serum pentobarbitone level greater than 40 mg/l.

2. Pentobarbitone

The total dose of pentobarbitone given varied between 1.4 and 4.0 g or 19-57 mg/kg, with a mean of 2.25 g or 34.2 mg/kg. Serum levels of pentobarbitone during clipping of the aneurysm varied between 15 and 55 mg/l with a mean of 31 mg/l. The CFM trace was flat in all but two cases, which showed a burst-suppression pattern. There was no consistent relationship between serum levels and activity seem on the CFM trace. A response to surgical retraction on the CFM trace persisted in all cases at all times (Fig. 2).

3. (i) Non-Barbiturate Group - Neurological Results

The overall immediate postoperative combined mortality and morbidity or complication rate in the 86 non-barbiturate cases was 22.2%. In order to eliminate from these results the contribution made by recurrent haemorrhage in cases where no clip could be placed, we shall confine our attention throughout this report to cases where a clip was placed. In the 69 non-barbiturate cases where a clip was placed the complication rate was 21.7% (Table 1). About three quarters

Table 1. Overall results in 69 clipped non-barbiturate cases

Dead	3	21.7%
Permanent new deficit	12	
Transient deficit	2	78%
Uncomplicated	52	

of the cases were clinically uncomplicated postoperatively. Cases so classified do not include those with a transient new neurological deficit. An isolated new third nerve paresis following internal carotid artery (ICA) aneurysm surgery is not counted here as a new neurological deficit.

Table 2 shows a breakdown of the 69 clipped non-barbiturate cases with respect to the anatomical location of the aneurysms. Anterior communicating artery (ACoA) cases here include aneurysms of the A_1A_2 junction as well as those arising from the anterior communicating artery itself. Anterior cerebral artery

Table 2.* Results in 60 non-barbiturate cases with respect to anatomical location of aneurysm.

	MCA	ICA-bif	ICA	ACoA	ACA	Total
Dead	1	1	1	0	0	3
ND	4	3	2	2	1	12
TD	1	1	0	0	0	2
U	2	5	16	25	4	52
%U	25	50	84	92.5	80	75.4
Total	8	10	19	27	5	69

* ND denotes a permanent new focal neurological deficit; TD denotes a transient neurological deficit; U denotes a total absence of clinical complications; other abbreviations see text.

(ACA) here denotes aneurysms of the distal ACA; ICA denotes aneurysms arising at the level of the posterior communicating artery and ICA-bif. denotes aneurysms at the bifurcation of the internal carotid artery into the anterior and middle cerebral arteries. Among eight cases where the aneurysm was situated at the bi- or trifurcation of the middle cerebral artery (MCA) there was one death and four permanent new neurological deficits, a complication rate of 62.5%. Two cases ran a clinically uncomplicated course. Among ten ICA-bifurcation cases there was one death and three new deficits, a complication rate of 40%; fifty percent of cases were clinically uncomplicated postoperatively. Of nineteen ICA cases 84% were totally uncomplicated and among 27 ACoA cases 92.5% were uncomplicated with a complication rate of 7.4%. There were only five aneurysms of the distal ACA; one developed a permanent new neurological deficit.

3. (ii) PentobarbitoneCases - Neurological Results

The overall results for 23 pentobarbitone cases where a clip was placed are shown in Table 3. The overall combined mortality and morbidity was 17%.

Table 3. Overall results in 23 clipped pentobarbitone cases

Dead	2	17%
Permanent new neurological deficit	2	
Transient deficit	3	83%
Uncomplicated	16	

Table 4.* Results in 23 barbiturate cases with respect to anatomical location of aneurysm.

	MCA	ICA-bif	ICA	ACoA	ACA	Total
Dead	0	0	1	1	0	2
ND	0	1	1	0	0	2
TD	2	1	0	0	0	3
U	6	0	7	1	2	16
%U	75	0	78	50	100	69.5

* Abbreviations - see Table 2.

These results are broken down with respect to location of the aneurysms in Table 4. The greatest difference between the pentobarbitone and non-barbiturate results appears in cases involving the MCA. The complication rate among eight non-barbiturate MCA cases was 62.5% as compared to zero among eight pentobarbitone MCA cases. This is significant according to Fisher's exact probability test, $p = 0.0265$. There were only two pentobarbitone ICA-bifurcation cases, of which one developed a permanent new neurological deficit related to occlusion of the middle cerebral artery at its origin following intraoperative rupture of the aneurysm; the other had a transient deficit. Among nine ICA cases the complication rate was 22% (Table 5).

Table 5*. Results of cases involving the middle cerebral artery

	No barbiturates				Pentobarbitone	
	MCA		ICA-bif		MCA	ICA-bif
Total	8		10		8	2
Dead	1	62.5%	1	40%	0	0
ND	4		3		0	1
TD	1		1		2	1
U	2		5		6	0
%U	25		50		75	0

* Abbreviations - see Table 2.

4. Preoperative State

Fifteen non-barbiturate cases were in Hunt and Hess' grade III or IV (84) preoperatively, of which eight or 53% either died or sustained a new neurological deficit in the immediate postoperative period. Among the MCA and ICA-bifurcation cases, five were in grade III or IV preoperatively, of which all developed a new deficit or died. Six out of nine non-barbiturate ICA, ACoA and ACA cases in grade III or IV preoperatively had no permanent postoperative sequelae.

In the pentobarbitone group three MCA cases were in Hunt and Hess' grade III or IV preoperatively without developing any deficit postoperatively.

The difference between the outcomes in non-barbiturate and pentobarbitone MCA cases in preoperative Hunt and Hess grade III or IV is significant according to Fisher's exact probability test, $p = 0.046$.

5. Interval from Subarachnoid Haemorrhage to Surgery

The interval from the last subarachnoid haemorrhage to surgery was longer than 14 days in all the non-barbiturate MCA cases. One non-barbiturate ICA-bifurcation case had a two day interval and developed a permanent new deficit postoperatively. All pentobarbitone cases involving the MCA had an interval of 18 days or more. One pentobarbitone ICA case with a two day interval and with severe, global cerebral vasospasm died (see below).

6. Mortality and Morbidity

(i) Non-barbiturate group: 15 cases: Occlusion of the distal ACA following rupture of an ACA aneurysm resulted in a permanent new hemiparesis in one case; in one ACoA case occlusion of an ACA at its origin was followed by massive cerebral oedema and ultimately by a residual neurological deficit. Severe vasospasm unrelated to aneurysm rupture was seen in one case and in seven cases the aneurysm ruptured intraoperatively. In some of these marked vasospasm was recorded after the clip was placed. Three cases had been in Hunt and Hess' grade II or IV preoperatively but had no other recognizable factors predisposing them

to risk. One ICA-bifurcation case was one week postpartum and thus probably in a hypercoagulable state, on account of which hypothermia was not used (no angiograms are available for this case). One ACoA case had no attributes of note except for a different surgeon.

(ii) Pentobarbitone group: 4 cases: All four complications in this group followed intraoperative rupture of the aneurysm. One death occurred in an ICA case who was soporose (Hunt and Hess grade IV) with severe, global cerebral vasospasm preoperatively and where recurrent haemorrhage had taken place two days prior to surgery. The second death was due to massive pulmonary embolism in an ACoA case where both anterior cerebral arteries had been occluded by clips (also other surgeon). One new neurological deficit was the result of occlusion of the MCA at its origin following intraoperative rupture in an ICA-bifurcation case; the last had a delayed onset (ICA case without preoperative angiography).

7. Cerebral vasospasm and its consequences

The overall incidence of angiographically documented vasospasm during surgery not associated with intraoperative aneurysm rupture was $^{4}/_{50}$ in the non-barbiturate group and $^{31}/_{18}$ in the pentobarbitone group (Table 6).

Table 6. Incidence and sequelae of vasospasm*.

Nobarbiturates (69):	4 vasospasm, no rupture	2 ND
	6 rupture + vasospasm	2 dead
		2 ND,
		1 TD
	13 rupture "alone"	1 dead,
		3 ND,
		1 TD
Pentobarbitone (23):	3 vasospasm, no rupture	1 TD
	3 rupture + vasospasm	1 dead,
		2 TD
	1 rupture "alone"	1 ND

* Abbreviations - see Table 2.

The sequelae to vasospasm in the non-barbiturate group as a whole, regardless of whether or not this was associated with intraoperative aneurysm rupture, and assuming that rupture is invariably followed by a degree of vasospasm, include three deaths, seven permanent new neurological deficits and two transient deficits, a combined mortality and morbidity of $^{10}/_{23}$ = 43%. If thirteen cases where intraoperative rupture occurred without explicit documentation of vasospasm are excluded, then it is seen that six out of the ten remaining cases either died or developed a permanent deficit.

In the pentobarbitone group one case with severe, global vasospasm died and in one ICA case who developed a new deficit following intraoperative rupture no

angiography was performed. There were no permanent sequelae to marked segmental vasospasm in five cases: following rupture in two cases and in the absence of rupture in three cases. A complication rate following vasospasm with or without rupture of 10 out of 23 non-barbiturate cases thus compares with 2 out of seven pentobarbitone cases.

Considering now cases involving the middle cerebral artery separately, *i.e.*, MCA and ICA-bifurcation cases (Table 7), vasospasm in the absence of

Table 7*. Incidence and sequelae of vasospasm in cases involving MCA

Non-barbiturate	No rupture	Rupture
8 MCA	4: 3 vasospasm/2 ND	4: 1 ND, 1 dead
10 ICA-bif	4: nil	6: 2 ND, 1 dead
Pentobarbitone	**No rupture**	**Rupture**
8 MCA	7: 1 vasospasm + TD	1: vasospasm + TD
2 ICA-bif	0	2: 1 vasospasm + TD, 1 ND (vascular occlusion)

* Abbreviations - see Table 2.

aneurysm rupture was recorded in three out of eight non-barbiturate cases and in one out of seven pentobarbitone cases. Intraoperative rupture occurred in ten non-barbiturate cases of which five either died or developed a permanent new deficit. When these ten cases are assumed to have had a degree of vasospasm following rupture, the incidence of permanent sequelae to vasospasm among non-barbiturate cases is seen to be 7/13 or 54%. This compares with four cases of rupture or vasospasm in the pentobarbitone group, of which one developed a new deficit; this was related to vascular occlusion and not to vasospasm (see above). It is thus possible that the incidence of vasospasm not associated with intraoperative aneurysm rupture and of the sequelae to vasospasm may be lower in the pentobarbitone MCA and ICA-bifurcation cases than in non-barbiturate cases. However, the number of pentobarbitone cases is at present too small for the difference between the two groups to reach statistical significance.

8. General Clinical Observations

The quality of recovery in pentobarbitone cases was generally excellent. Many patients were able to go home seven to ten days postoperatively in spite of having spent the first day or two on a ventilator. One ICA case developed severe cerebral oedema during emergence from pentobarbitone but subsequently recovered uneventfully following a second administration of pentobarbitone. In one case occlusion of a branch of the MCA resulted in no clinically recognizable neurological deficit, although a CT scan four days postoperatively showed cerebral oedema with a marked midline shift (Fig. 3). In another ICA case severe

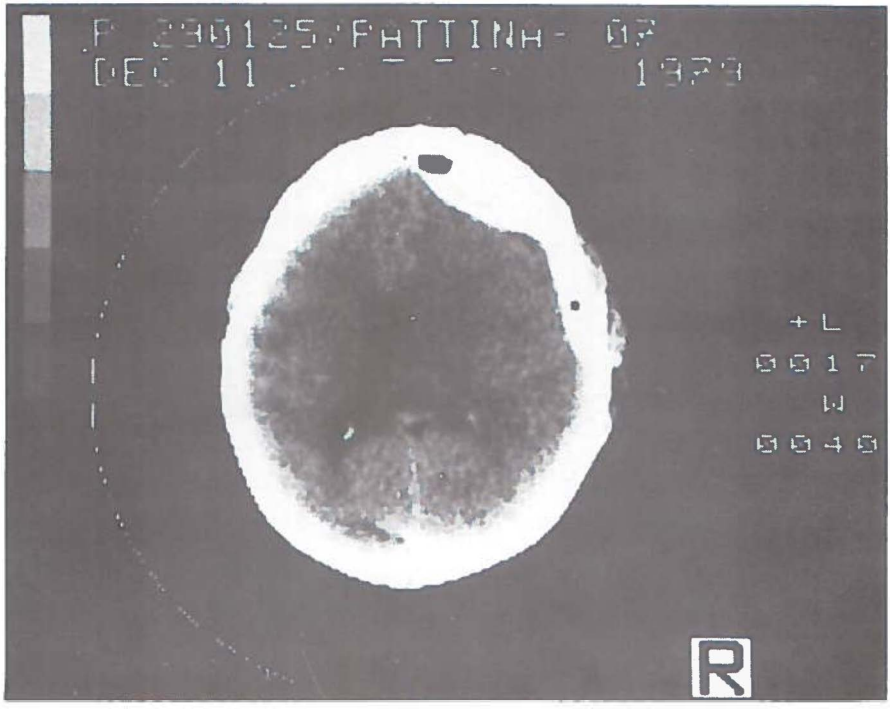

Fig. 3. Computer tomography scan 4 days postoperatively in a pentobarbitone loaded MCA case where an MCA branch was occluded during surgery. No clinical manifestations.

spasm of the distal ICA and of at least the A_1 segment of the ACA followed clipping of the aneurysm so that the ACA was not visible after rewarming (Fig. 4). The patient made an uneventful recovery.

Non-neurological complications in three cases may be at least partly attributed to the use of barbiturates with a prolonged period of postoperative immobility: one patient died as the result of massive pulmonary embolism, another developed a deep vein thrombosis two weeks postoperatively and there was one case of pulmonary infection which delayed the patient's extubation for more than 24 hours.

Discussion

The poor results in the non-barbiturate MCA cases contrast with those of non-barbiturate ACoA cases. Poor results for MCA aneurysms are reported by a number of authors including Krayenbühl (95), Nornes and Wikeby (154), Rasmussen et al. (168) and Artiola et al. (9), but not by others including Hugosson (80), Saito et al. (178) and Gonski et al. (60). Differences in surgical

Fig. 4a. Peroperative angiogram performed on the day of operation in a pentobarbitone loaded ICA case. Anterior cerebral artery – A; aneurysm – B.

Fig. 4b. Peroperative angiogram after clipping and rewarming in the same case, showing clip (arrow) and severely spastic distal ICA (arrow-heads). ACA is not visible.

technique, patient selection and management may account for the variation in these results.

Although there is little difference in outcome between clipped cases in the pentobarbitone and non-barbiturate groups overall, a significant difference is seen when MCA cases are considered separately. Here, a complication rate (or combined mortality and morbidity) of 62.5% in the non-barbiturate cases compares with zero in the pentobarbitone cases. This difference is significant according to Fisher's exact probability test, $p = 0.0256$. Since there are only two ICA-bifurcation cases in the pentobarbitone group they cannot be considered alone; when ICA-bifurcation cases are considered together with MCA cases (as cases involving the middle cerebral artery) a complication rate of 50% in the non-barbiturate group compares with 10% in the pentobarbitone group ($p = 0.08$). Moreover, this 10% represents a case of arterial occlusion by a clip.

The difference in results between non-barbiturate and pentobarbitone MCA cases is not readily accounted for by a difference in the proportion of high risk cases in the two groups, that is, in preoperative Hunt and Hess grades III and IV cases, nor by the number of cases with a short haemorrhage-to-surgery interval. A systematic difference between the two groups which cannot be eliminated is that the pentobarbitone cases were ventilated for 16 to 46 hours postoperatively while the non-barbiturate cases were not. Immobilisation and ventilation at normocarbia were found by Bleyaert et al. (27) to be beneficial in primates following an episode of global ischaemia. It remains uncertain to what extent this difference could have contributed to our results.

Because the MCA supplies the pre- and postcentral gyri and Broca's area, ischaemia and infarctions in its territory produce limb weakness, hemiparesis or dysphasia. These focal deficits are well defined and easy to identify and are therefore more likely to be accurately and reliably recorded than, for instance, a psychological change. This is particularly true when cases are considered retrospectively. The high incidence of complications among the non-barbiturate MCA cases will also tend to highlight any improvement accompanying the use of barbiturates. Considering MCA cases alone further reduces the inhomogeneity among cases, although their numbers are much reduced. Simple conventional statistical tests do not take this into account.

The ACA also contributes to the arterial supply of the motor cortex pertaining to the leg. The small number of distal ACA aneurysm in this study does not allow assessment of the possible benefits of pentobarbitone therapy in these cases.

Our results are consistent with the experimental work of Selman et al. (184) who observed no amelioration of the effects of permanent occlusion of the MCA at its origin in the baboon by barbiturates. They are also broadly comparable with those of Hoff et al. (74) who gave pentobarbitone during aneurysm surgery with hypothermia in four cases of permanent and three cases of temporary arterial

occlusion. Three of the four cases with permanent occlusion developed neurological deficits while a temporary occlusion of 90 minutes duration did not result in a deficit. We have seen no apparent beneficial effect of barbiturates in the presence of severe, global vasospasm. As experimental studies have led us to expect, pentobarbitone appears to be effective in incomplete, focal ischaemia where some flow either remains or is maintained via a collateral supply or where the ischaemia is of limited duration.

Hoff et al. (75) and Corkill et al (45) describe a protective effect of barbiturates which is dose related. It is perhaps only a matter of curiosity to note in this context that all the pentobarbitone cases in our study who dveloped serious postoperative complications had peak serum pentobarbitone levels of less than 25 mg/l, while the case with severe spasm of the ACA which recovered uneventfully had a peak level of around 50 mg/l. In the case where an MCA branch was occluded without clinical sequelae the peak serum pentobarbitone level was 29 mg/l and in the four cases who had transient deficits the peak level ranged from 29 to 40 mg/l.

The figures for the incidence of cerebral vasospasm in our cases cannot be regarded as reliable for a number of reasons. A much slowed blood flow associated with cerebrovascular constriction is common at 27° to 29°C. In a number of cases severe segmental vasospasm seen at these temperatures immediately after clipping was subsequently seen to resolve on rewarming to 35°C. Vasospasm should thus strictly be considered to be present only if it persists after rewarming. However, angiography was not repeated in all cases after rewarming when vasospasm was recorded at hypothermic temperatures nor was it repeated postoperatively. On the other hand, vasospasm may develop postoperatively after a delay, perhaps following intraoperative aneurysm rupture or manipulation, while not evident immediately after clipping. In a few cases angiograms were not available and in some ICA cases no angiography was performed. These considerations may explain in part why the difference in the incidence and sequelae of vasospasm between the non-barbiturate and pentobarbitone groups is not as clear as the difference between the outcomes. Vasospasm presumably is responsible for cerebral ischaemia which produces a large proportion of the complications of aneurysm surgery. We are, however, satisfied that the risk of developing vasospasm is not increased by the use of pentobarbitone together with moderate hypothermia.

Psychological assessments were made in a number of patients both pre- and postoperatively but were not sufficiently standardized or systemic to allow presentation here. Preoperative assessment is complicated by the enforcement of bed rest and the frequent need for sedation and postoperative assessment by the effects of frontal lobe retraction which the frontal approach entails. However, our observation of the generally excellent quality of recovery usually seen in pentobarbitone cases leads us to speculate that careful and systematic

psychological testing might reveal better results in the pentobarbitone-loaded ACoA and ACA cases than in non-barbiturate cases.

The anaesthetic technique we have described in this paper involves little added risk to the patient when adequate monitoring is employed and is no more troublesome during surgery than conventional techniques. Our results suggest any added risk to the patient and extra work load for the medical and nursing personnel in the postoperative period is likely to be justified for aneurysms involving the middle cerebral artery, which appear to be particularly prone to complications and where we have seen a significant improvement using pentobarbitone. It can only be speculated that a comparable improvement may be seen in aneurysms of the distal ACA and that psychological complications might also be shown by suitable testing to be reduced by prophylactic pentobarbitone loading. We feel that our results so far are encouraging and that these aspects deserve further evaluation.

CHAPTER IV
NEUROMONITORING

CHAPTER IV.1

Cerebral Function Monitoring as a guide to high dose barbiturate therapy for cerebral protection in focal cerebral ischaemia

A. Buchthal and M. Belopavlovic

There has been much interest in recent years in the possible therapeutic applications of high doses of barbiturates, following the demonstration that they are capable of ameliorating the effects of focal cerebral ischaemia in primates in experimental conditions (75, 132, 144, 184). This effect of barbiturates, as well as their protective effect in mice exposed to hypoxia (5, 8, 201, 202) is distinct from and apparently independent of their action relieving intracranial hypertension by reducing cerebral oedema, since it is seen in the absence of the latter. The cerebral protective effect of barbiturates is seen when they are given either before an episode of focal cerebral ischaemia or within a limited time after its onset (44, 185) and there is some evidence that their effect is dose related (75). There is now considerable doubt as to their value in global ischaemia (29, 57, 105, 204, 226). Most reports of clinical results of high dose barbiturate therapy have so far concerned patients with severe head injury (117, 169, 170, 189, 232, 237) and metabolic encephalopathy (115, 236). Here, relief from intractable intracranial hypertension was the primary objective. More recently, barbiturates have been use in carotid endarterectomy (64, 198) and have been found to be effective in reducing the incidence of neuropsychiatric complications following cardiopulmonary bypass (155), where at least a part of the morbidity is thought to be the result of embolic phenomena, i.e., multifocal in origin. However, although barbiturates are apparently in use for cerebrovascular surgery in a number of centres (23, 197), there has been no evaluation of their effectiveness in this situation apart from a preliminary report by Hoff et al. (74) on seven patients and the report from this Clinic by the present authors (see Chapter III.3). In none of the clinical applications of barbiturates to date has there been general agreement as to which barbiturate is the most effective and suitable for clinical use, its optimal dosage or the criteria which should determine dosage and the duration of

therapy. The present investigation was undertaken to provide insight into these questions.

While serum barbiturate levels have been used as a guide to therapy (187), they are well known to be an unreliable index of the depth of cerebral depression because of the existence of acute and chronic tolerance (7, 63, 197, 202). When relief of intracranial hypertension is the primary objective, intracranial pressure values together with the cerebral perfusion pressure and the intracranial pressure-volume response may reasonably be used as a guide to barbiturate dosage and duration of therapy (115, 117, 170, 237). However, in a number of reports systemic arterial hypotension accompanying the use of barbiturates in high doses has limited the dosage in clinical practice (36, 227, 232). This has led to the recommedation of the use of a burst-suppression EEG pattern as an end point criterion for the dosage of barbiturates in clinical practice (90). The use of this criterion is supported by the experimental demonstration that the depression of cerebral oxygen consumption is maximal when the EEG becomes isoelectric under the influence of barbiturates: further increasing their dosage does not result in a further decrease in resting cerebral oxgen consumption (128). Since, in the presence of a burst-suppression pattern EEG, cerebral oxygen consumption is close to its minimum while arterial hypotension associated with higher doses is avoided, the burst-suppression pattern represents a good compromise as a criterion for dosage of barbiturates clinically and it has been widely adopted (185, 197, 322).

The use of the burst-suppression EEG pattern as a criterion for barbiturate dosage, however, presupposes that the beneficial effects of barbiturates are directly linked to their metabolic depressant effects. It is still not clear that this is indeed the case. This issue is discussed further in Chapters III.1 and IV.2. Evidence is presented here which suggests that functional neuronal depression is not maximal when the EEG is just rendered isoelectric and that barbiturates are capable of producing a far more profound functional depression in higher doses. The implications of this in clinical practice are discussed.

Patients, Materials and Methods

Cerebral Function Monitor

In all cases where barbiturates were given, cerebral activity was monitored continuously using the CFM during surgery and in the postoperative period.

The Cerebral Function Monitor (CFM) is an instrument designed in 1968 by Maynard, Prior and Scott (119) for use in patients resuscitated after cardiac arrest. It provides a continuous display of a signal derived from a single channel electroencephalogram (EEG) and therefore has many of the characteristics of the EEG.

A signal obtained from a single pair of biparietal scalp electrodes is subjected to heavy filtering, retaining only components between 2 and 15 Hz, and to logarithmic amplitude compression. The latter is necessary in order to cope with the large dynamic range of the EEG and to accentuate small changes in activity when the total activity is low. The processed signal is displayed and recorded on a chart recorder as a single trace at a slow speed and can be recorded continuously for long periods of time. The height of the trace is related to the total energy of the incoming signal, i.e., to both its amplitude and its frequency content, which thus cannot be distinguished. The width of the trace indicates the variability of the signal. A third electrode monitors the impedance between the two recording electrodes continuously.

Anaesthesia and surgery

Thirty three patients were given prophylactic barbiturates for intracranial aneurysm surgery. All were premedicated with atropine, pethidine, chlorpromazine and promethazine. Surgery was carried out under moderate hypothermia at 27°C to 29°C induced by surface cooling and with dexamethasone cover, 16 mg daily. A frontal approach was used with magnification. Cases were assigned to either of two groups according to whether they received sodium thiopentone or pentobarbitone.

Group I. Five patients received a single dose of 50 mg/kg sodium thiopentone over 30 to 40 minutes starting at the induction of anaesthesia. Anaesthesia was continued with pethidine, pancuronium and ventilation with nitrous oxide and oxygen. Controlled ventilation was continued postoperatively until the patients were awake.

Group II. Twenty eight patients received a similar premedication. Anaesthesia was induced with a sleep dose of etomidate and continued with pethidine, pancuronium and ventilation with nitrous oxide and oxygen. The technique is described in detail in Chapter III.3. Later, during cooling, a bolus of 600 mg pentobarbitone was given rapidly intravenously as a 1% solution, followed by a continuous infusion of 5 to 10 mg/minute. The rate of the infusion was adjusted to maintain a flat CFM trace until the neck of the aneurysm had been clipped. The total dose of pentobarbitone received by patients in this group therefore depended directly on their electrophysiological response to it and on the duration of the procedure. Sodium nitroprusside was used to control their arterial blood pressure. Hypothermia was induced and anaesthesia maintained otherwise as in Group I. Administration of pentobarbitone was discontinued after the aneurysm had been clipped and rewarming was begun. Controlled ventilation and all monitoring were continued postoperatively for as long as necessary, usually until the patients were awake.

Pentobarbitone was made available by the Pharmacy of the Academisch Ziekenhuis Groningen. Serum pentobarbitone levels were estimated by high performance liquid chromatography in the same Department.

Serum half-lives of sodium thiopentone and pentobarbitone were estimated after their discontinuation and after the initial rapid fall in their levels had taken place.

Evaluation of CFM records

The rate of recovery of cortical electrical activity after the administration of barbiturates was discontinued was measured as (R_3 - R_2): i.e., the time taken for the baseline of the CFM trace to reach 5μV (R_3) from the point at which it started to rise from the 0μV line (R_2). This is illustrated in Figure 1.

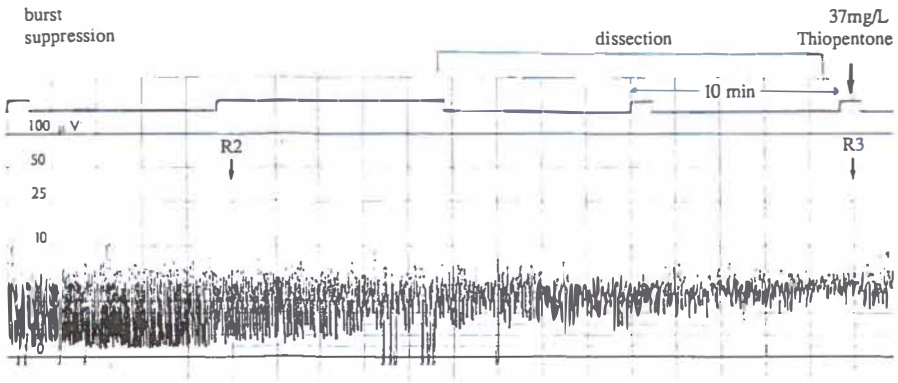

Fig. 1. Cerebral Function Monitor trace during dissection of aneurysm after a single loading dose of sodium thiopentone. A burst-suppression pattern is seen at the beginning of the record but the trace has left the baseline some time before dissection and clipping of the aneurysm. The interval: (R_3-R_2) is taken to estimate the rate of recovery of electrical activity. At R_2, the baseline of the trace begins to rise above 0μV; at R_3 the baseline reaches 5μV. Serum thiopentone level: 37 mg/L.

Results

Systemic arterial hypotension was not seen following a single loading dose of sodium thiopentone or in any case receiving pentobarbitone, even during hypothermia. Disturbances of cardiac rhythm were noted in several of the thiopentone cases. In both groups, sodium nitroprusside was invariably required during dissection of the aneurysm to control the arterial blood pressure.

Spontaneous cortical electrical activity was found to recover from a flat CFM record much faster after sodium thiopentone was discontinued than after discontinuing pentobarbitone. This is illustrated in Figure 2. After a single loading dose of sodium thiopentone, the CFM records in Group I were never flat during dissection and clipping of the aneurysm; indeed, cerebral activity had recovered to a large degree by this time (Figures 1 and 3).

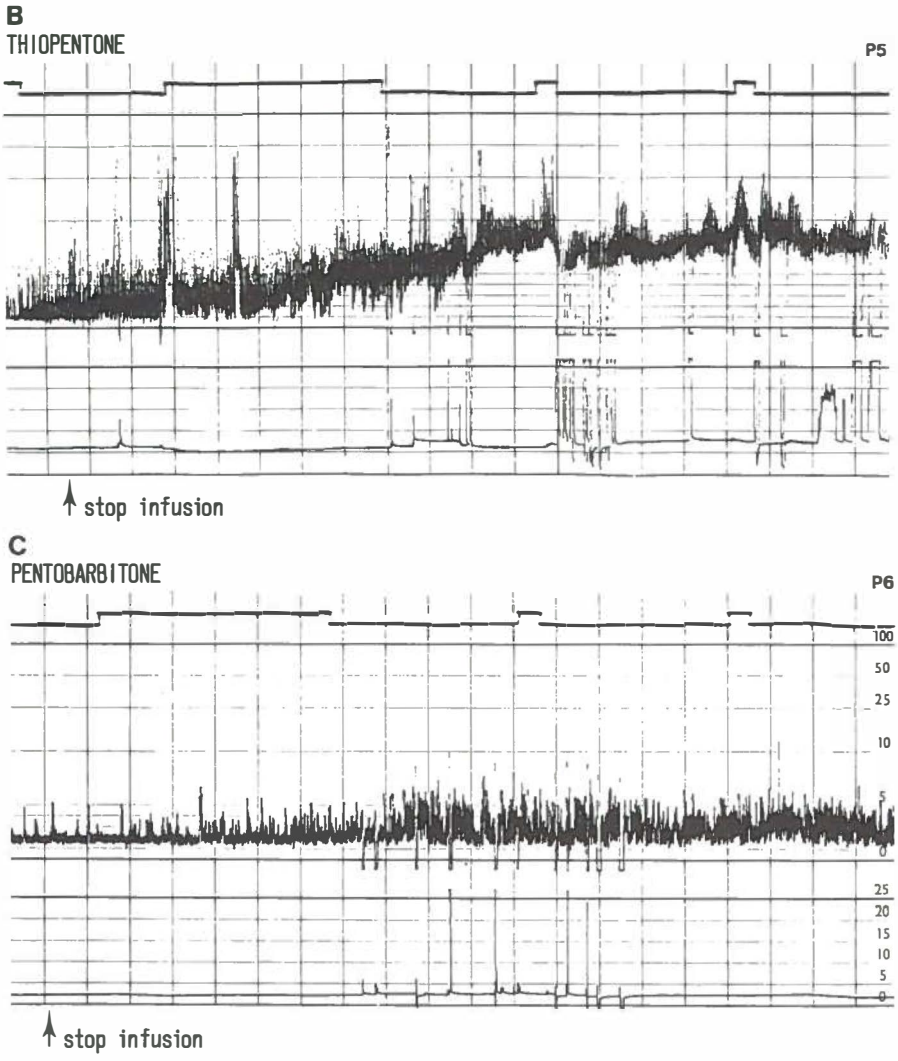

Fig. 2. Cerebral Function Monitor record on discontinuation of: B. Sodium thiopentone, and C. Pentobarbitone infusion. Time and amplitude scales as in Figure 1.

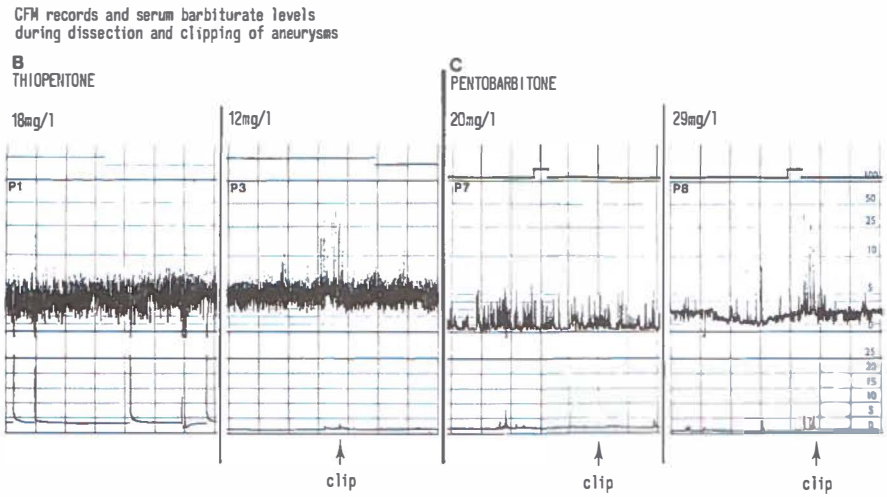

Fig. 3. Cerebral Function Monitor records and corresponding serum barbiturate levels during dissection of aneurysm in four cases, two after loading with sodium thiopentone and two during pentobarbitone infusion. Time scale as in Figure 1.

The total dose of pentobarbitone given to patients in Group II ranged from 19 to 57 mg/kg, mean: 33.6 mg/kg. Extracts from a typical CFM record from a pentobarbitone case are shown in Figure 4. A flat trace was obtained during dissection and clipping of the aneurysm in 24 of the 28 cases. In these, serum pentobarbitone levels associated with a flat trace ranged from 21 mg/L to 45 mg/L, mean: 32 mg/L. Serum pentobarbitone levels were not consistently related to cerebral activity either in the same patients at different times (Figure 5a) or in different patients with a similar degree of spontaneous cerebral electrical activity (Figures 5b, 5c).

No linear relationship could be demonstrated between extubation time and the rate of electrical recovery in Group I ($r=0.1$). In Group II, a weak relationship was found between extubation time and total dose of pentobarbitone ($r=0.47$) and no linear relationship was seen between extubation time and rate of electrical recovery ($r=0.15$) or serum half-life of pentobarbitone ($r=0.11$).

The 28 cases in Group II fall into three subgroups on an electrophysiological basis. Group IIa: In 4 cases the CFM trace was not flat during dissection of the aneurysm. This subgroup comprised one patient with a history of chronic alcohol abuse, one case which required postoperative ventilatory support for a pulmonary infection and two cases who became comatose again after recovering from the pentobarbitone load and were given pentobarbitone a second time. Group IIb: In 16 cases the CFM trace was flat in the absence of surgical

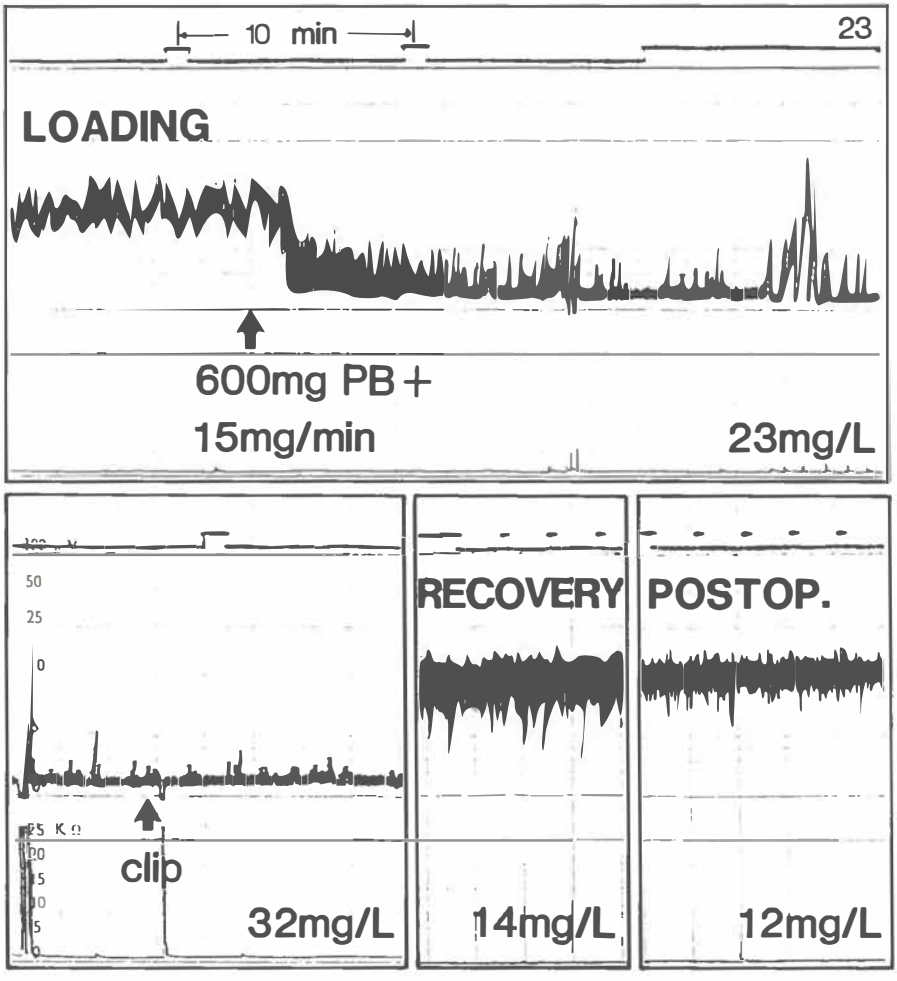

Fig. 4. Extracts of typical Cerebral Function Monitor recordings during cerebral aneurysm surgery with prophylactic pentobarbitone loading. Administration of pentobarbitone bolus and subsequent infusion rate are indicated on first record at start of loading. Corresponding serum pentobarbitone levels are shown below on each record. Note absence of spontaneous electrical activity at the time of clipping of the aneurysm: "clip".

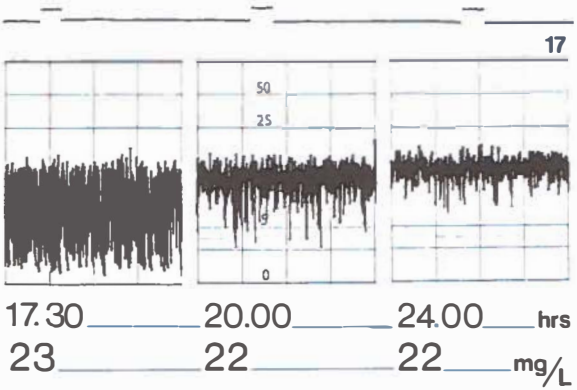

Fig. 5a. Postoperative Cerebral Function Monitor records after cerebral aneurysm surgery from one patient at three different times during recovery, showing serum pentobarbitone levels which do not parallel the extent of spontaneous cerebral electrical activity. Time and amplitude scales as in Figure 1.

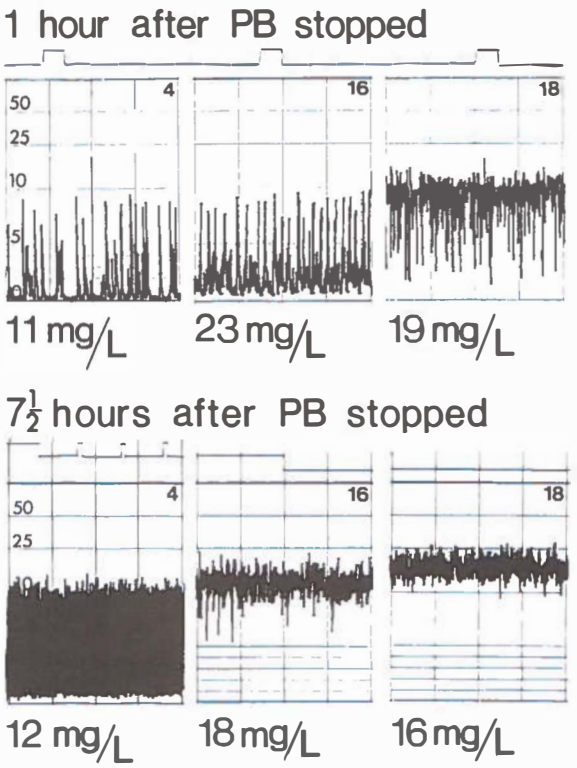

Fig. 5b and 5c. Cerebral Function Monitor records from three different patients after prophylactic pentobarbitone loading, at similar times after discontinuation of pentobarbitone infusion. 5b: one hour after end of infusion; 5c: 7.5 hours after end of infusion. Corresponding serum pentobarbitone levels are indicated below each record. Time and amplitude scales as in Figure 1.

manipulation during the period of dissection of the aneurysm. An electrical response to surgical retraction remained in all cases; in eight, this was accompanied by acute arterial hypertension. Such an electrical response is illustrated in Figure 6. The acute haemodynamic response was followed by aneurysmal rupture in four cases. Group IIc: In eight cases, the highest pentobarbitone levels measured during dissection were higher than those seen to be associated with a flat trace earlier. Responses to retraction persisted in every case. There were two cases of rupture of the aneurysm before it could be clipped.

The mean dose of pentobarbitone, peak serum levels, the rate of electrical recovery (R_3 - R_2), serum half-life of pentobarbitone and postoperative extubation times, together with the incidence of intraoperative aneurysmal rupture in subgroups IIa, IIb and IIc, are summarised in Table 1.

Table 1.

Mean subgroup	IIa	IIb	IIc
Dose pentobarbitone, mg/kg (SD)	22	33.8 (8.9)	35.7 (16.7)
Peak serum level, mg/L (SD)	20	30.9 (6.8)	36.4 (10.2)
Recovery rate (R_3-R_2), min (SD)	91.7	99.25 (59.3)	225.6 (190.2)
Serum Pb half-life, min (SD)	11.5	13.7 (11.3)	33.1 (43.1)
Extubation time, hours (SD)	19	37.6 (11.1)	43.75 (12.8)
Aneurysm rupture	1 (25%)	4 (28%)	2 (20%)

Data for 28 cases loaded prophylactically with pentobarbitone.
Group IIa: EEG not flat during dissection - 4 cases
Group IIb: EEG flat during dissection - 16 cases
Group IIc: Higher peak serum levels during disscetion than seen to be associated with flat EEG - 8 cases.

Six cases in Group II had been treated with diazepam preoperatively. Their mean extubation time was 40.3 hours, with a mean pentobarbitone dose of 43.4 mg/kg and mean rate of electrical recovery 178.8 minutes, compared to 39.5 hours, 33.56 mg/kg and 131.3 minutes respectively in the other cases who had neither a history of alcohol abuse nor received diazepam preoperatively.

Discussion and conclusions

The wide discrepancies between serum pentobarbitone levels and the degree of depression of spontaneous cortical electrical activity shown by our cases is at least partly the result of tolerance phenomena which are well known (7, 63, 179, 202). Etomidate was used as the anaesthetic induction agent in Group II in order to avoid exposure to a barbiturate and thus induce acute tolerance before loading with pentobarbitone. The ability of etomidate to induce cross-tolerance to a barbiturate after a single dose is, however, not known. Six cases who received diazepam preoperatively showed scattered and inconsistent rates of electrical recovery and extubation times, so that the extent of development of tolerance

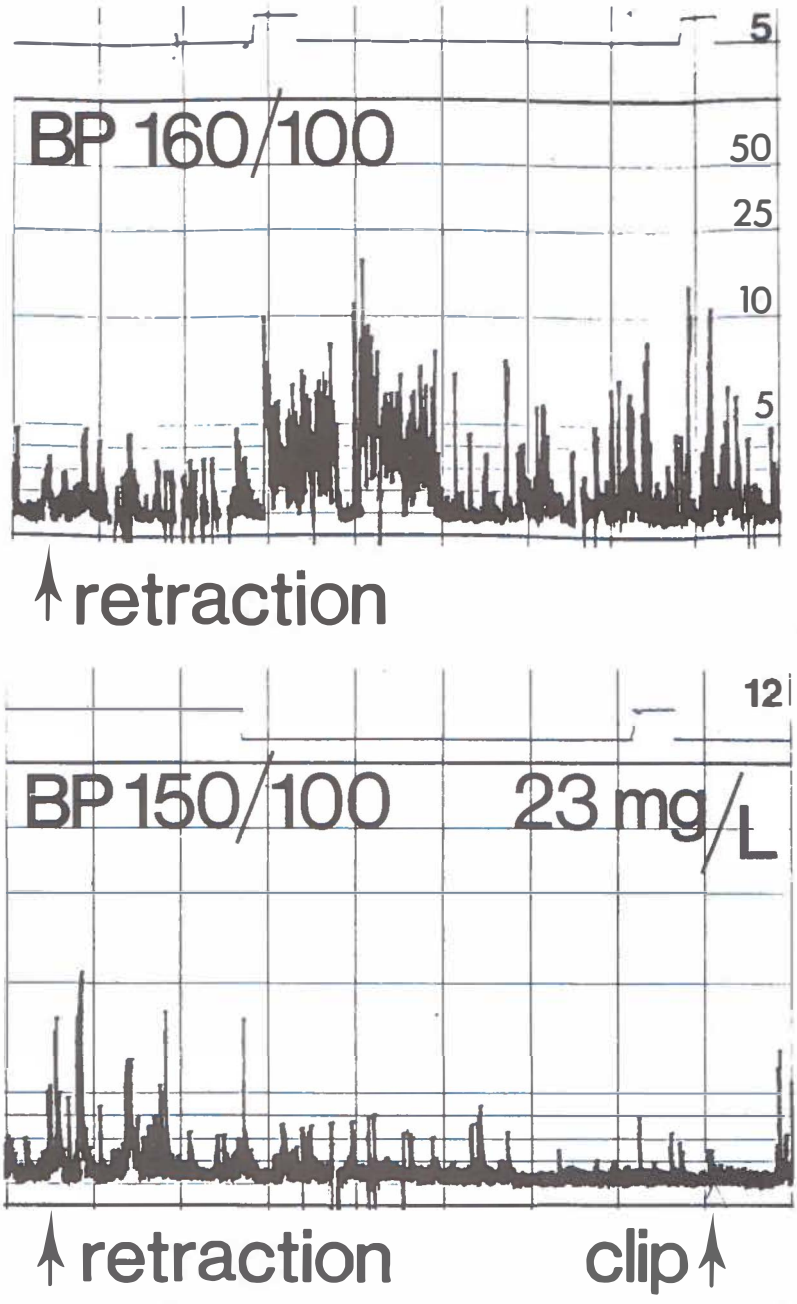

Fig. 6. Cerebral Function Monitor records during dissection of an intracranial aneurysm in two cases. Arterial blood pressure before retraction: above, 90/60; below, 110/75, rising to 160/100 and 150/100 respectively on brain retraction in the presence of sodium nitroprusside infusion. Time scale as in Figure 1. Serum pentobarbitone level during lower record is indicated at top right of recording. Note cerebral electrical response to retraction in each case accompanied by sharp rise in arterial blood pressure.

may be variable and other factors may contribute to a variable response to a given dose of a barbiturate. Among other known variables is the concentration of barbiturate reaching the brain. The pK of pentobarbitone is 7.6 so that the ionised fraction will be strongly pH-dependent at a physiological pH. Since only the non-ionised fraction crosses the blood-brain barrier readily, blood-brain partition coefficient will also be strongly pH-dependent. The pH of cerebrospinal fluid (CSF) is lower than that of blood and is raised by acute hyperventilation. When the arterial carbon dioxide tension is held low for many hours, however, CSF-pH returns towards normal values, thereby increasing the fraction of barbiturate able to reach the brain. The degree and duration of hyperventilation is therefore another variable influencing the concentration of barbiturate reaching the brain, as well as the rate of its renal eliminiation. It is not our practice to employ more than a mild degree of hyperventilation (arterial carbon dioxide tension 4.0-4.5 kP).

Plainly, total serum barbiturate levels are not a reliable guide to the cortical depressant effect of barbiturates and a direct index of cortical function is preferable. The literature provides some evidence that cerebral protection by barbiturates in hypoxia and in focal cerebral ischaemia parallels functional cerebral cortical depression (128, 133), Steen et al. (201) demonstrated the protective action of methylphenobarbitone in hypoxic mice to be linked to its anaesthetic effect, since the + isomer of the drug lacks both properties to a significant degree. Tolerance to the anaesthetic effect of barbiturates parallels reduced resistance to hypoxia in the same model (202). Observations reported here indicate that anaesthetic depth and functional cerebral depression are not maximal under the influence of barbiturates: an electrical response to surgical retraction persisted even where barbiturates were given in excess of the dosage required to flatten the EEG, sometimes accompanied by acute hypertension. The persistence of an evoked response under these conditions is supported by reports describing the persistence of the brainstem auditory evoked potential (200, 50, 176) and the somatosensory evoked potential (209, 56) in the presence of doses of barbiturates more than adequate to flatten the EEG. Comatose patients receiving barbiturates have been sucessfully monitored in this way (82, 108, 150). Returning to barbiturate protection, Hoff et al. (75) obtained the smallest infarcts in baboons following middle cerebral artery occlusion when using 128 mg/kg pentobarbitone, while approximately 50 mg/kg are necessary to flatten the EEG. The clinical results of the cases discussed here are described in Chapter III.3, and are consistent with the contention that the dose dependence of barbiturate protection in focal cerabral ischaemia extends to much higher doses than are needed to produce an isoelectric EEG.

The possible remains, therefore, that cerebral protection in focal cerebral ischaemia may be more complete when very large doses of barbiturate are used.

Doses of upto 57 mg/kg pentobarbitone were well tolerated by our cases: no hypotension was seen even at 28°C. In contrast, disturbances of cardiac rhythm encountered with a moderate dose of sodium thiopentone, together with the observation that a single dose produces profound cerebral depression for only a very short time, indicates that this barbiturate is less suitable for clinical use than pentobarbitone, since it will be poorly compatible with a diminished cardiovascular reserve or with hypothermia. For these reasons, the use of a single, loading dose of sodium thiopentone was abandoned after five cases.

Figure 7 shows a compressed spectral array presentation of the EEG from one of the cases in Group II during dissection of the aneurysm. It is evident that, when the EEG is flat, this monitoring technique can provide no indication of the presence or absence of disturbances of cerebral function which might allow avoiding action to be taken without delay. Monitoring of event related potentials is the only means of assessing cerebral function under these circumstances.

It is concluded from the observations considered here that:

1. Pentobarbitone is preferable to sodium thiopentone in clinical practice for high dose barbiturate therapy;
2. Pentobarbitone may safely be given in doses in excess of those required to flatten the EEG without risk of hypotension, even at 28°C;
3. The EEG is useful as a guide to effective barbiturate dosage for cerebral protection in focal cerebral ischaemia, and should be kept completely flat for this purpose;
4. A flat EEG does not represent a state of maximal functional cerebral cortical depression, at least in the presence of barbiturates;
5. It is possible that the most complete cerebral protection can be obtained by the use of very large doses of barbiturate, i.e., far in excess of those which flatten the EEG.

Summary

Thirty three patients were given prophylactic sodium thiopentone or pentobarbitone for intracranial aneurysm surgery under moderate hypothermia with Cerebral Function Monitor control. A single loading dose of 50 mg/kg sodium thiopentone tended to produce disturbances of cardiac rhythm and the EEG depression it produced was very short lived. In contrast, pentobarbitone in doses exceeding those necessary to flatten the EEG were not associated with disturbances of cardiac rhythm or with arterial hypotension at 28° - 29°C. Serum barbiturate levels were not consistently related to the degree of EEG depression. When the EEG was flat under the influence of pentobarbitone, a cortical electrical response to surgical retraction persisted in all cases, sometimes associated with acute arterial hypertension. The implications of these findings are discussed with respect to cerebral protection in focal cerebral ischaemia.

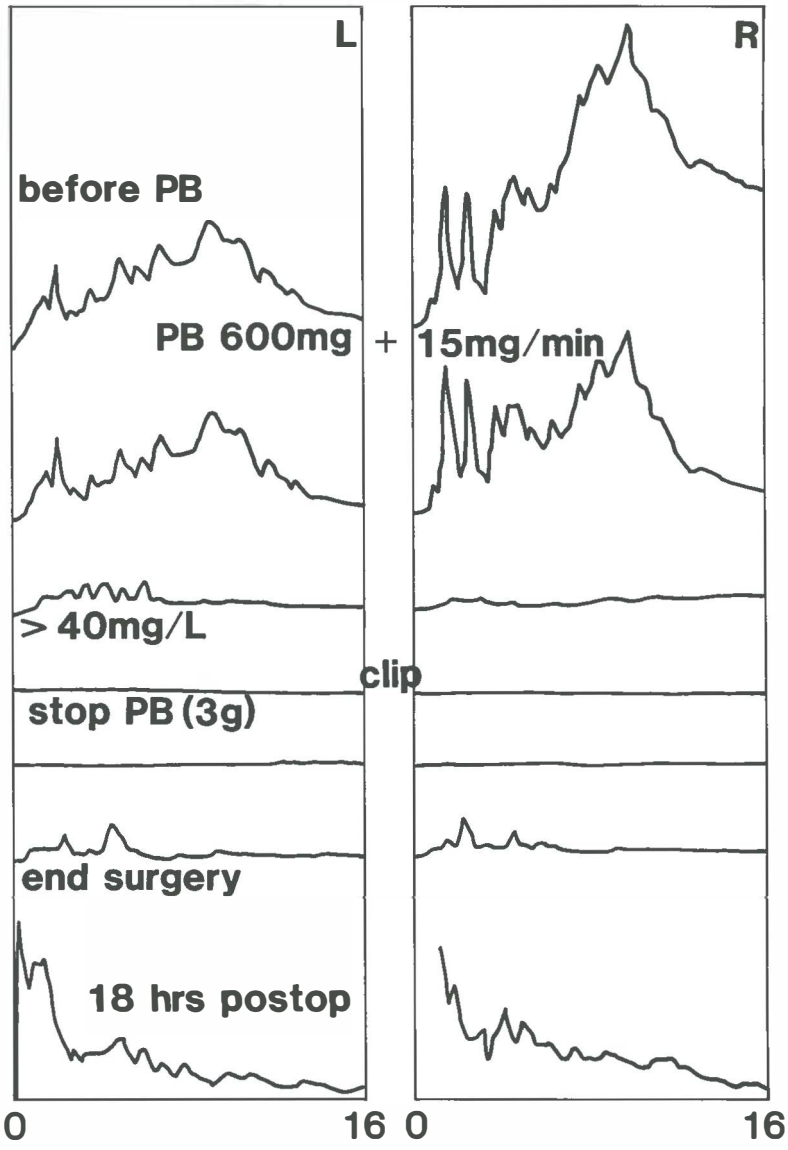

Fig. 7. Compressed spectral array display of bilateral parietal EEG in a case loaded with pentobarbitone. Recordings from left hemisphere on left side, from right hemisphere on right side. Frequency base: 0-16 Hz. Pentobarbitone infusion starts with 600 mg bolus and is continued at the rate indicated below top record. Serum pentobarbitone level at the time of third record was over 40 mg/L. Clip was placed at the time of 4th record, following which the pentobarbitone infusion was discontinued. Total pentobarbitone dose is indicated below 4th record. Note absence of spontaneous cerebral activity during placement of clip on the neck of the aneurysm and slow postoperative recovery of electrical activity.

CHAPTER IV.2

Evoked potentials in cerebral aneurysm surgery

A. Buchthal and M. Belopavlovic

Introduction

One of the issues traditionally surrounding neurological surgery and anaesthesia is the difficulty of neurological assessment under anaesthesia or during controlled ventilation with sedation. Many neurosurgeons have felt this consideration to be overriding and have insisted on spontaneous respiration throughout surgery of the posterior fossa, relying on the spontaneous respiratory pattern as an indicator of brain stem function. This practice is by no means extinct today.

In the last decade, barbiturates have been used clinically in doses which flatten the EEG or produce a burst-suppression pattern in the management of intractable hypertension and fulminating cerebral oedema intraoperatively (188), in severe head injuries (117, 170, 237) and in metabolic encephalopathy (55, 115). They have also been used prophylactically in the absence of cerebral oedema in cerebrovascular surgery (18, 22, 74, 98, 122, 197) and in carotid endarterectomy (64, 198). The experimental basis for their use in focal ischaemia of limited duration is provided by the work of Selman and his co-workers on monkeys (184), following a volume of both primate and non-primate experimental work involving middle cerebral artery (MCA) occlusion (75, 132, 144, 201, 238).

During deep barbiturate sedation the difficulties are compounded. Cranial nerve reflexes and pupil reactions are attenuated or absent. In addition, pentobarbitone, which can be used safely in high doses without haemodynamic instability seen with thiopentone, has a much longer duration of action which runs into days after a single loading dose rather than hours. This may be beneficial to the patient but is unlikely to be welcomed by the surgeon in the absence of adequate means of neurological assessment. Assessment can be achieved with multimodal evoked potential monitoring (50, 56, 82, 108, 150, 209). More recently, somatosensory evoked potentials (SEP) have been used to monitor cerebral function intraoperatively during aneurysm surgery (93, 125, 223). In particular, monitoring of a topographically specific area of the cerebral cortex supplied by the parent artery of an aneurysm by means of the SEP can allow the surgeon to employ safely a period of occlusion of that vessel in order to facilitate dissection of that aneurysm. This technique, which has been used together with hypothermia in the past (30, 162, 211, 212) is now again being increasingly

employed (103, 141, 214, 219), usually without hypothermia. Temporary vascular occlusion is more effective in reducing the tension in the arterial walls than is a degree of systemic arterial hypotension commonly used for the purpose, while avoiding the potential hazard of hypotension (61, 101, 156). Temporary occlusion also reduces the risk of intraoperative aneurysmal rupture to a minimum. This unfortunate event is almost invariably followed by vasospasm leading to cerebral ischaemia which can be severe enough to result in massive cerebral oedema and even in tentorial herniation (14).

Patients with aneurysms associated with the MCA carry a high perioperative risk in many reported series and have been shown to benefit most from prophylactic barbiturates in high doses (20). In the case of the MCA, functional integrity of the sensory cortex representing the palm of the hand together with the intervening pathway can conveniently be monitored using the SEP in response to stimulation of the contralateral median nerve at the wrist.

The three MCA aneurysm cases presented here illustrate these developments in the management of cerebral aneurysm surgery. The first case shows the feasibility of carrying out routine intraoperative SEP monitoring in the presence of a dose of pentobarbitone which flattens the EEG and the consequences of intraoperative aneurysm rupture. The second case illustrates the manner in which the SEP can be used as a guide to permissible MCA occlusion time when the surgeon makes use of temporary MCA occlusion, and in the third case the two techniques of SEP monitoring during high dose barbiturate administration and temporary MCA occlusion are combined.

Case 1

A man aged 28 years was admitted following an episode of subarachnoid haemorrhage (SAH), accompanied by severe headache, vomiting and generalised convulsions. There was no focal neurological deficit on admission the same day. He was known to have familial polycystic kidneys bilaterally with good renal function and had been treated for hypertension in the past with clonidine and a low salt diet. He also had a mild pulmonary valvular stenosis and insufficiency. A CT can revealed an intracerebral haematoma and blood in the left Sylvian fissure. Angiography showed an aneurysm arising at the first bifurcation of the left MCA.

He underwent surgery four days post-SAH, with antibiotic prophylaxis and dexamethasone cover, 16 mg daily starting 24 hours preoperatively. Immediately preoperatively he started to develop neck stiffness and to become increasingly drowsy. A catheter was introduced into the left internal carotid artery by the Seldinger technique for intraoperative angiography. He was premedicated with a lytic cocktail (chlorpromazine 50 mg, pethidine 50 mg, promethazine 25 mg and

atropine 0.5 mg) and anaesthesia was induced with etomidate and suxamethonium chloride. It was continued with pethidine and pancuronium and ventilation with nitrous oxide and oxygen. Moderate hypothermia was induced by surface cooling ("Blanketrol", Cincinnati Sub-zero); sodium nitroprusside was used to promote peripheral vasodilatation and aid cooling and to control the arterial blood pressure (SABP) when necessary. Arterial carbon dioxide tension was maintained at 4.0 to 4.5 kP when estimated at 37°C and a condenser humidifier was employed until rewarming was begun, when heated gases were delivered via a Bennett Cascade humidifier.

Cerebral activity was monitored using a Cerebral Function Monitor (CFM), (Devices), as described by Maynard et al. (119). A signal obtained from biparietal scalp electrodes is subjected to heavy filtering and semi-logarithmic amplitude compression and is displayed as a single, continuous trace on a chart recorder. The deflection is related to the total power of electrical activity between 2 and 15 Hz in the close vicinity of the electrodes. The width of the trace indicates the variability of the signal, which increases with deeping anaesthesia. A third electrode monitors impedance between the two recording electrodes; this was kept below 3 kΩ at all times.

SEP in response to median nerve stimulation at the wrist were recorded using silver-silver chloride skin contact electrodes at C_3' and C_4' locations according to the international 10-20 system, and over the cervical spine, with a frontal reference electrode. Square wave pulses of 200 μsec were delivered at a rate of 3 to 7 per second with 10-12 mA using skin contact electrodes. Nicolet CA 1000 equipment was used to average 500 responses. SEP were evaluated using the central conduction time (CCT) described by Hume and Cant (81), i.e., the interval between the peak recorded over the cervical spine and the N20 peak at the cerebral cortex.

Surgery was carried out via a left pterional, trans-Sylvian approach using microsurgical techniques. On the basis of the increased risk of vasospasm associated with his deteriorating level of consciousness and of surgical intervention on the fourth day post-SAH, it was decided to load with pentobarbitone prophylactically. On opening the dura, a large haematoma was found surrounding the aneurysm. The proximal M1 segment of the MCA* was seen to be somewhat spastic. Pentobarbitone administration was begun after the dura was open with a bolus of 600 mg followed by an infusion of 7.5 mg/min of a 1% solution. Pentobarbitone was supplied by the Hospital Pharmacy. The infusion rate was adjusted to keep the CFM trace as nearly flat as possible throughout dissection of the aneurysm and was discontinued 125 minutes after

* The M1 segment of the MCA extends from the origin of the MCA at the internal carotid artery bifurcation to its first bifurcation.

the aneurysm had been clipped. A total dose of 2.0 g or about 30 mg/kg was given. No drop in SABP was associated with its use. In spite of the use of sodium nitroprusside, the aneurysm ruptured before it could be clipped with the loss of about 1L of blood. After clipping the aneurysmal neck, the MCA remained narrow, filling poorly on angiography. Papaverine 5% was applied locally.

Intraoperative recordings from this case are shown in Figure 1. The amplitude of the SEP is little affected by the combination of moderate hypothermia and pentobarbitone in this dosage. The CCT lengthened progressively from record (1) to record (3) as the temperature fell; at the end of surgery in record (4) it was shorter at 35°C than in record (3) at 27.9°C, but longer than in the initial record (1) under the influence of pentobarbitone. No marked difference in CCT or in N_{20} peak latency between the two hemispheres was seen at any time. The CFM trace, which was virtually flat during dissection of the aneurysm, recovered promptly on discontinuing the pentobarbitone infusion and after 20 minutes the trace rose from the baseline.

During closure, an epidural pressure transducer was implanted in one of the craniotomy burr holes for postoperative monitoring. After completion of surgery and rewarming, controlled ventilation was continued for 40 hours, when the patient was awake and extubated. There was a slight weakness of the right arm and right facial muscles at this time.

The following day, however, he became increasingly drowsy and dysphasic with increasing weakness of the right arm, becoming comatose with extensor rigidity and hyperpyrexia. A CT scan showed massive oedema of the left hemisphere with a marked midline shift. The craniotomy bone flap was removed as a decompressive measure and pentobarbitone given again. This time a bolus of 400 mg was followed by an infusion of 150 mg/hour for four days. At the same time, 20% mannitol was given by infusion for three days with twice daily frusemide and 5% human albumin. On the second day of pentobarbitone administration the SEP was present in the left hemisphere with a 3 msec delay of the N_{20} peak with respect to the right side. He was awake and extubated 48 hours after discontinuing the pentobarbitone infusion. On the day preceding extubation the N_{20} peak was delayed by 1.5 msec on the left with respect to the right hemisphere. Power in the right arm improved steadily and on discharge there was minimal weakness and apraxia of the right hand. He was able to resume his former employment as a technician.

Case 2

A 54 year old housewife who had previously been well was first seen in the Neurosurgical Department ten days after SAH. At the time of SAH, there had been a severe headache of sudden onset with pain radiating to the right shoulder

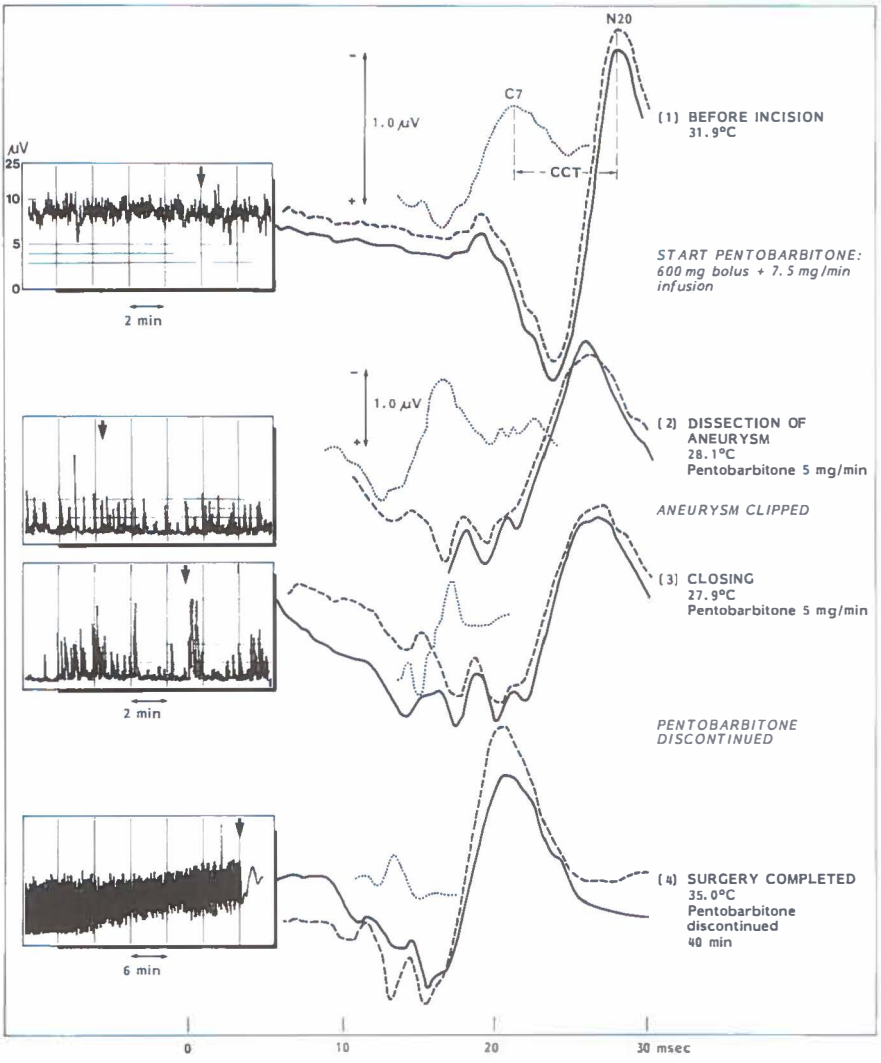

Fig. 1. Intraoperative recordings in case 1 of Cerebral Function Monitor (CFM) (left) and somatosensory evoked potentials (SEP) (right).
A. Temperatures are nasopharyngeal throughout. SEP are recorded negative upwards. The N_{20} peak and central conduction time (CCT) are marked on the first record. Solid lines were recorded from the operated hemisphere, interrupted lines from the non-operated hemisphere and dotted lines over the cervical spine. Only one of the two cervical waveforms is shown for the sake of clarity.
B. Amplitude scale of CFM traces is shown on the first record and is the same throughout. Vertical arrows on CFM traces indicate approximate times of the corresponding SEP recording.
C. Amplification of SEP recording (1) is twice that in subsequent recordings. The CFM trace in record (1) is consistent with surgical anaesthesia. In record (2), it is depressed to the baseline with occasional spikes. In record (3), the CFM trace is flat with occasional interference or response to surgical stimulation. The time scale of the CFM trace is compressed in record (4), where the trace starts to rise from the baseline about 20 minutes after discontinuing pentobarbitone.

and arm and neck stiffness, together with protracted vomiting. When, four days later, the headache continued to be severe with photophobia, she was admitted to her local hospital. There was some disturbance of memory and tingling in the fingers of both hands. CT scan revealed blood in the right Sylvian fissure and angiography showed aneurysms at the bifurcation of both MCA's. There was an hour-glass constriction of the right internal carotid artery 1 cm proximal to its bifurcation.

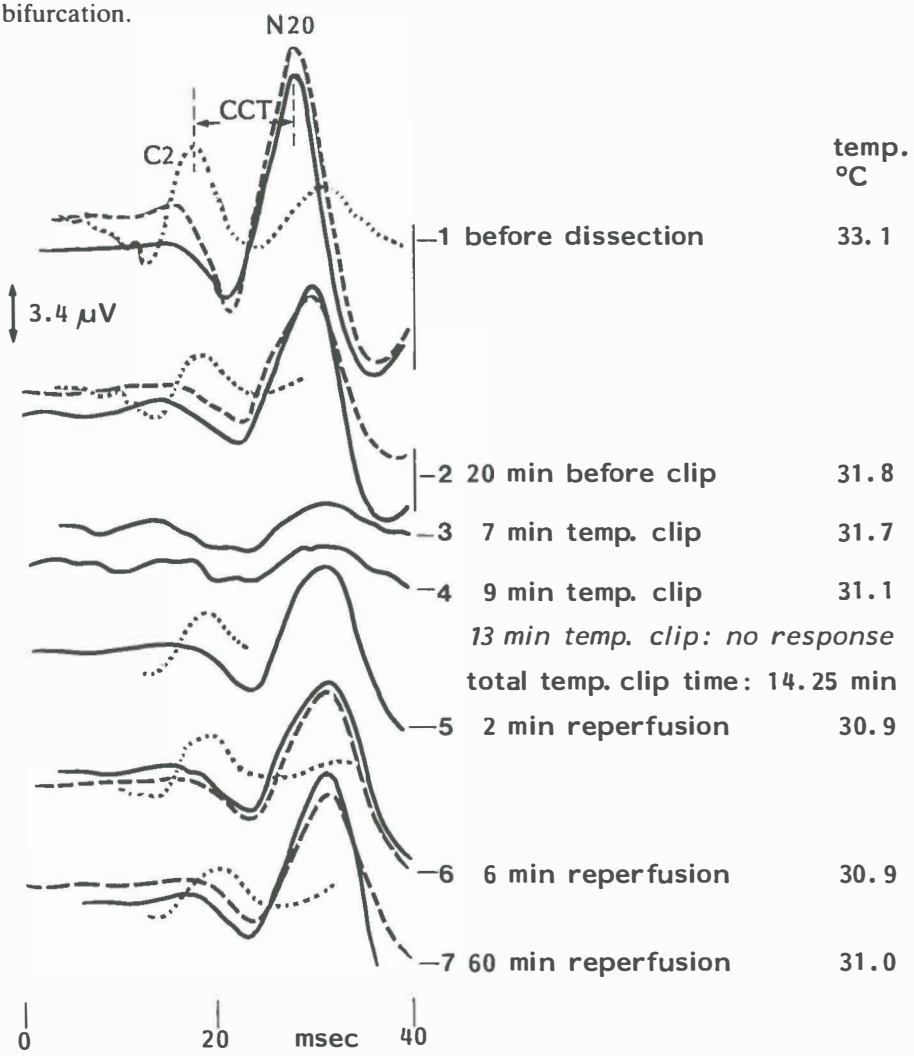

Fig. 2. Intraoperative recording in case 2.
See Legend to Figure 1, A.
B. SEP was present, though much reduced in amplitude, after 9 minutes' MCA occlusion, After 13 minutes' occlusion the N_{20} peak could not be identified (no record). Two minutes after releasing the temporary clip the SEP recovered substantially.

Surgery was performed on the right MCA aneurysm first but this was postponed until 27 days post-SAH due to persistent vasospasm. She was prepared for surgery in the same way as Case 1. Surgical and anaesthetic techniques and SEP monitoring were carried out as described above. Pentobarbitone loading was not carried out in connection with a change in surgical technique, as follows. During the final stage of dissection, the distal M1 segment of the MCA was occluded with a temporary Aesculap clip about 5 mm proximal to its termination and distal to the origin of the proximal lateral striate arteries. During the period of occlusion, SABP was raised to a high normal level. The nasopharyngeal temperature was 31.1°C. Intraoperative SEP recordings are shown in Figure 2. After 7 minutes' occlusion (record 3), the N_{20} peak was much reduced in amplitude and was delayed by 1.28 msec with respect to its pre-clip latency (record 2). After 13 minutes' occlusion the N_{20} peak could no longer be identified: unfortunately, no permanent record of this waveform was made. The temporary clip was removed after 15 min 15 sec occlusion, when the aneurysm had been clipped. Two minutes later the amplitude of the SEP had recovered (record 5). After one hour's reperfusion the CCT was the same in the two hemispheres (record 7). Postoperatively, there was no neurological deficit.

Case 3

A women of 21 years was admitted six weeks after the second of two episodes of SAH, with an interval of a week between the episodes. There had been no loss of consciousness or neurological deficit during either episode. A CT scan showed an intracerebral haematoma and angiography revealed two aneurysms arising from the right MCA: a bilobar aneurysm at the first MCA bifurcation (M1/M2 junction) and another at the second MCA bifurcation distally (M2/M3 junction). Preoperatively there was no neurological deficit or depression of conscious level. Preoperative and anaesthetic management were as in case 1 and surgical technique was as described in case 2. It was decided to use prophylactic pentobarbitone on the basis of the increased risk associated with two MCA aneurysms. It was administered after the dura was open as described in case 1: a bolus of 600 mg was followed by an infusion of 10 mg/min which was adjusted to keep the CFM trace flat during dissection of the two aneurysms. To facilitate the final stages of dissection of each, a temporary Aesculap clip was placed on the distal M1 segment of the MCA. The first of these was in place for 28 minutes and was released when the proximal, bilobar aneurysm was clipped. There was then a period of 63 minutes of MCA reperfusion before applying the temporary clip for the second time. The distal aneurysm was much larger than had been indicated by angiography and the M3 segment of the MCA arose from it so that it proved impossible to clip this aneurysm without permanently occluding this branch of the

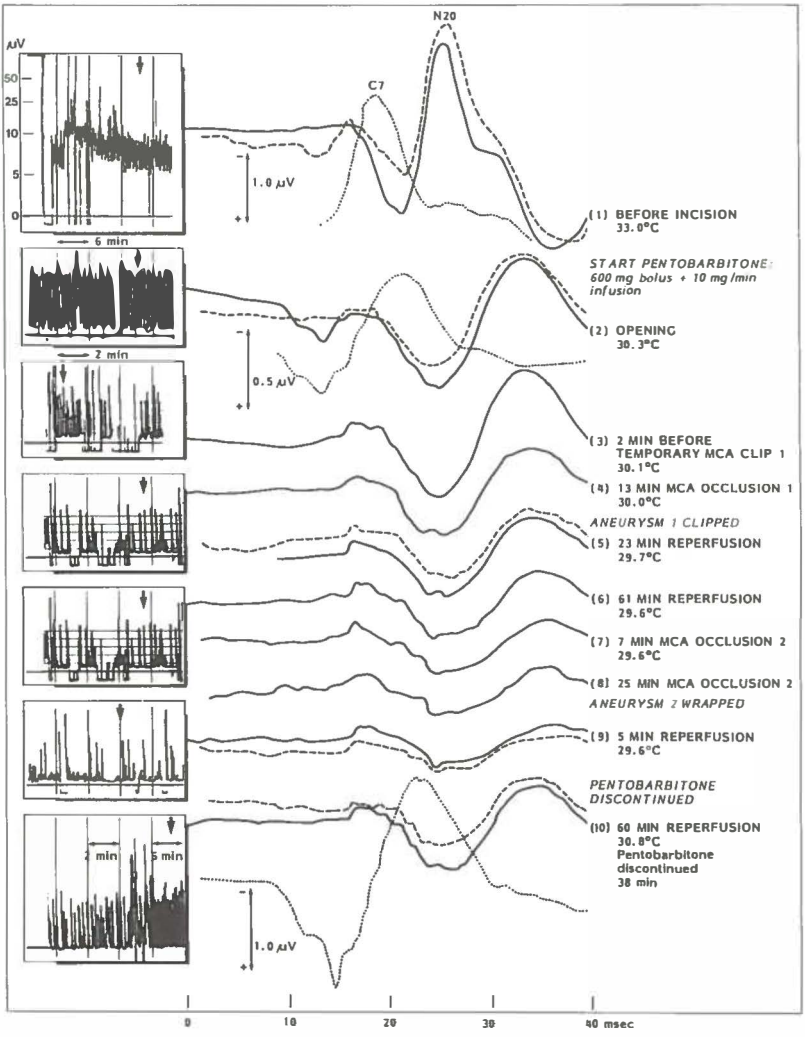

Fig. 3. See legend to Figure 1, A and B.
C. Amplification in SEP records (1) and (10) is one half that in (2) to (9). The height and width of the CFM trace in (1) is appropriate to surgical anaesthesia. Pentobarbitone administration is started after (1) and is continued until after (9). The CFM trace in (2) shows a burst-suppression pattern. Spontaneous electrical activity is further suppressed in (3) without marked change in the amplitude or latency of the SEP. The N_{20} peak in record (4) is delayed by 1.12 msec after 13 minutes' MCA occlusion at 30.0°C while the CFM trace is almost flat. After 23 minutes' reperfusion following 28 minutes of MCA occlusion, there is no difference in N_{20} peak latency between the two sides (5). During the second MCA occlusion period, no increase in N_{20} peak latency occurs between 7 and 25 minutes of occlusion (7) and (8). No marked left-right difference is seen after 5 minutes reperfusion - (9), while the amplitude of the waves is much reduced and the CFM trace is flat. The SEP amplitude recovers to previous levels as a burst-suppression pattern returns some 20 minutes after pentobarbitone is discontinued.

MCA. The aneurysm was coated with fibrin and wrapped with muscle. The second temporary clip was in place for 29 minutes at a nasopharyngeal temperature of 29.4°C. Peroperative angiography following wrapping of the second aneurysm showed minimal vasospasm. As in case 2, the administration of sodium nitroprusside was stopped and the SABP allowed to rise to high normal levels during each period of MCA occlusion.

The pentobarbitone infusion was discontinued 22 minutes after the release of the second temporary clip. The total dose given was 2.7 g or 44 mg/kg. Intraoperative recordings in this case are shown in Figure 3. As seen in record (4), there was no delay of the N_{20} peak after 13 minutes of MCA occlusion relative to that in the pre-occlusion record (3) and no further delay occurred within the period of occlusion. In the second period, similarly, there was little delay after 25 minutes although the amplitude of the SEP was much reduced in both hemispheres at this time. The patient was rewarmed during closure and ventilation was controlled for 68 hours postoperatively, after which time she was fully awake with no neurological deficit. The postoperative course was clinically uneventful.

Discussion

The first case illustrates a number of points in the management of cerebral aneurysm patients.

Intraoperative rupture is a recognised hazard in aneurysm surgery (14). It is almost invariably followed by vasospasm which can be long lasting and severe, causing ischaemia which results in massive cerebral oedema. This may be followed by infarction or by tentorial herniation or both, as in the first case. The MCA is notoriously prone to become spastic on manipulation, which is necessarily more extensive after anuerysmal rupture. A number of centres report a higher complication rate with MCA aneurysms than with those in other locations (9, 20, 95, 134, 168).

Blood breakdown products are known to play a part in the development of vasospasm, which begins to manifest itself 3 to 4 days post-SAH or postoperatively. There is at present still no drug therapy which is effective in alleviating established vasospasm. There have been some positive reports using calcium entry blockers prophylactically (6, 12, 13, 159) and with a new thromboxane synthetase inhibitor (215). Aggressive intravascular fluid loading with or without hypertension induced by aminophylline and isoprenaline can be effective in reducing the clinical manifestations of vasospasm (53, 77, 91, 94, 140, 165, 196) but carries the risk of exacerbating vasogenic oedema formation as well as that of intracranial haematoma formation and of haemorrhagic infarction postoperatively (224). Surgical intervention between the third and the seventh

day post-SAH is usually considered to be unwise if there is evidence of developing vasospasm, since this is then very likely to be troublesome postoperatively (30, 49, 79, 84, 105). However, this risk must be weighed against that of death from recurring SAH if surgical intervention is delayed.

The risk of intraoperative aneurysm rupture can be reduced to a minimum by temporary occlusion of the parent artery, as in cases 2 and 3. This avoids prolonged regional cerebral hypoperfusion which is likely to occur during systemic arterial hypoptension after SAH, particularly in the presence of vasospasm (52), when cerebral autoregulation is defective so that perfusion is totally pressure dependent (217). As mentioned above, cerebral complications are not unknown after systemic hypotension (61, 101, 156). While some leptomeningeal-cortical collateral circulation has been demonstrated in the monkey (216) and residual flow during MCA occlusion can be maximised by raising SABP (since this, again, is pressure dependent), the results of Suzuki and his colleagues using this technique indicate that monitoring of the ischaemic territory during the occlusion is mandatory (214). They report 32 MCA aneurysm cases where the MCA was occluded at normothermia for less than 15 minutes of whom 4 cases (12.5%) developed a permanent postoperative neurological deficit, whereas in 50 cases with 15 to 30 minutes' occlusion, 44% had a permanent postoperative deficit. Both groups received 20% mannitol, which had been shown to prolong permissible cerebral arterial occlusion time (213).

The suitability of SEP as an indicator of cerebral ischaemia and, thus, of "safe" cerebrovascular occlusion times, is provided by experimental work on monkeys. This has established several distinct thresholds of local cerebral blood flow (rCBF) using transorbital MCA occlusion in monkeys. Below a flow of 23 ml/100 g/min down to about 18 ml/100g g/min, fully reversible paralysis occurred in awake monkeys. If a flow of 18 ml/100 g/min or less is maintained indefinitely, infarction occurred (87). Lower flows were tolerated for progressively shorter times, infarction occurring when rCBF fell below 12 ml/100 g/min for 1½ to 2 hours (110, 143). In the anaesthetised baboon, the SEP starts to decline at flows below about 20 ml/100 g/min and is abolished at 15 ml/100 g/min, which is known as the threshold for synaptic transmission or of electrical failure (35, 11). Here, viability is maintained for a limited time, while infarction with massive release of intracellular potassium occurs at still lower flows, which define a threshold for membrane failure. In SAH patients, Rosenstein et al. (171) have found that the CCT is prolonged in proportion to the reduction in flow when this falls below a mean hemispheric CBF of 30 ml/100 g/min.

There thus appears to be a margin of flow where the SEP is affected but full functional recovery occurs if flow is restored within a limited time. It is possible to release the temporary clip during surgery if failure of the SEP indicates this to be

necessary. In our experience, up to three minutes of MCA occlusion are tolerated at 28° - 30°C after the SEP has failed without neurological sequelae. Nevertheless, the reliability of the SEP in indicating adequate residual flow during MCA occlusion must be qualified. Only one sensory pathway, from the palm of the hand to the sensory cortex representing it, is monitored. Inhomogeneities of perfusion within the territory of the MCA may be accentuated during its occlusion, due, for instance to distal segmental narrowing or vasospasm. Regional ischaemia not affecting this pathway will not be detected. Further, although occlusion of the distal M1 segment spares many of the perforating arteries, some of the 402 perforating arteries described by Umansky at al. (229) as arising from the M1 segment of the MCA will be perfused only by residual flow during its occlusion. These may supply subcortical structures not involved in the median nerve-to-sensory cortex pathway, ischaemia of which will again not be detected. On the other hand, the flow thresholds of subcortical structures lie at lower values than those of the neocortex (32). The distribution of CBF following MCA occlusion in the monkey has been described by Symon et al. (222). However, it should be noted that transorbital occlusion performed in many experimental studies is a proximal occlusion and cannot be strictly compared to the distal M1 segment occlusion employed in the cases discussed here as regards subcortical ischaemia.

The routine use of moderate hypothermia for cerebrovascular surgery has continued in our Department since the 1960's largely as a result of surgical preference. At 28°C, cerebral oxygen consumption is approximatley one half of that at 37° so that the "safe" vascular occlusion time is doubled (174). Twenty eight minutes is, however, rather longer than twice the duration of total cerebral circulatory arrest known to be tolerated at 37°C. This lends support to the contention that incomplete ischaemia is less damaging than complete ischaemia (203).

In the third case, occlusion times of 28 and 29 minutes were tolerated at 30.3° C and 29.6°C respectively, with 44 mg/kg pentobarbitone, without marked asymmetry of the SEP between the two hemispheres. Residual perfusion following MCA occlusion is known to vary widely between individuals, and this patient probably had a collateral circulation which was better than average. Hypothermia and barbiturates are known to potentiate each other's cerebral metabolic depression in dogs (96). This is generally thought to be linked to the protective effect of barbiturates. However, Branston et al. (31) could not demonstrate a lowering of the flow threshold for the abolition of the SEP or for intracellular potassium release in the baboon under the influence of 14 mg/kg pentobarbitone, although Selman and Spetzler (184) did demonstrate a lengthening of permissible transorbital MCA occlusion time in baboons with 30 mg/kg pentobarbitone. Although barbiturate-induced cerebral metabolic

depression is maximal when the EEG becomes isoelectric, Hoff et al. (75) have demonstrated a dose-related protective effect in MCA occlusion in the baboon extending to 128 mg/kg, over twice the dose which flattens the EEG. Further, far higher doses of barbiturates are needed to suppress short latency cortical and subcortical evoked responses than will abolish spontaneous cortical activity: an isoelectric EEG evidently does not represent a state of maximal functional depression under the influence of barbiturates, in spite of the fact that resting oxygen consumption has reached a minimum (128). Although barbiturates do affect the CCT and the amplitude of the early cortical peak of the SEP, the waveform remains intact at over twice the dose needed to flatten the EEG (50, 56). The same is true for short latency auditory evoked potentials (190). These considerations call into question the use of the burst-suppression pattern of the EEG as an end-point criterion for barbiturate dosage in cerebral ischaemia in clinical practice, as this is based on the depression of cerebral oxygen consumption in dogs (90).

The delayed development of severe cerebral oedema in the first case after his initial recovery from surgery and pentobarbitone loading perhaps calls for some comment. This phenomenon has been seen on several occasions in our Department when barbiturates were withdrawn in the presence of persisting vasospasm and resembles the uncontrollable rise in intracranial pressure on discontinuing barbiturates in severe head injury patients described by Yano et al. (237). In retrospect, it would have been preferable to continue barbiturate administration until there was evidence of resolution of vasospasm. Vasospasm of the major cerebral arteries can now be readily assessed at the bedside by means of non-invasive transcranial Doppler techniques (1, 2) using portable equipment. Unfortunately, this was not available to us at that time.

The Figures illustrate that the CCT is strongly temperature dependent, as has previously been described (83). However, temperatures during dissection of the aneurysm are quite stable with our technique and there is likely to be little difference in the temperature of the central pathway between the two hemispheres. Volatile anaesthetic agents, however, cause dose-related changes in the CCT and in the amplitude and latency of the N_{20} (124, 158, 181, 231). If they are used to control the SABP during aneurysm surgery, any changes in their concentration made for this purpose could interfere with the assessment of the adequacy of cortical perfusion by means of the CCT, although changes again will be symmetrical. Brown et al. (37) have reported that the N_{20} could not be identified in three out of eight volunteers receiving 2% isoflurane in air (end-tidal). Although such concentrations are not necessary for the maintenance of anaesthesia they may be needed for induced hypotension.

It has been suggested the dose-related changes in the short latency components of the SEP may provide a means of assessing the depth of anaesthesia (181).

Whereas this may be true for the volatile agents, it is clearly not the case where barbiturates are concerned.

Evoked potentials have been used for neurological assessment in comatose patients, including barbiturate coma (50, 56, 82, 108, 150, 209). In the first case discussed here, SEP provided the first indication of recovery during the second administration of pentobarbitone. Multimodal evoked potential monitoring in the presence of deep barbiturate sedation is likely to pave the way to the more widespread use of barbiturates in those cases where experimental evidence and clinical experience indicates this may be of value. These include focal cerebral ischaemia of limited duration, severe cerebral oedema and head injury cases seen to be neurologically intact immediately after the injury but deteriorating later in the absence of a mass lesion ("talk-and-die" cases), when therapy can be started without delay.

The third case described here illustrates the feasibility of combining the two techniques used in the first two cases. In this way, a patient at special risk can benefit from both approaches designed to lower the perioperative risk of cerebral aneurysm surgery.

It is to be anticipated that the technique of temporary cerebral arterial occlusion with topographically specific evoked potential monitoring will be extended to other major cerebral arteries using appropriate sensory pathways. This technique is readily employed in the presence of very deep barbiturate sedation. We conclude that intraoperative evoked potential monitoring is likely to make a valuable contribution to patient safety during cerebral aneurysm surgery.

Summary

Evoked potentials provide a convenient means of neurological assessment in patients under deep barbiturate sedation. This may be employed intraoperatively when a limited period of focal cerebral ischaemia might be expected. Further, topographically specific evoked potentials provide a means of assessing permissible cerebral arterial occlusion times during cerebral aneurysm surgery. Temporary occlusion of the parent artery of an aneurysm during its dissection is a great surgical convenience, avoids the need for systemic hypotension and minimises the risk of intraoperative aneurysm rupture. The latter is frequently followed by persistent and intractable vasospasm which is a major factor in perioperative morbidity in these patients. Three cases are presented which illustrate the use of somatosensery evoked potentials in cerebral aneurysm surgery.

CHAPTER IV.3

Somatosensory evoked potential monitoring in temporary middle cerebral artery occlusion during aneurysm surgery

J. J. A. Mooij, A. Buchthal and M. Belopavlovic
(Neurosurgery, in press, 1987).

Introduction

Temporary occlusion of parent arteries is now being increasingly employed in cerebral aneurysm surgery in order to facilitate the dissection of difficult aneurysms, as an alternative to systemic arterial hypotension (103, 214, 218). Temporary arterial occlusion is not only more effective than is systemic hypotension in reducing tension in the walls of the arterial structures while allowing normal perfusion of the remainder of the brain and of other organs, but also dramatically reduces the risk of intraoperative rupture during manipulation of the vessels. Moreover, systemic arterial hypotension can results in inadequate regional cerebral perfusion as a result of defective autoregulation which commonly follows subarachnoid hemorrhage (52, 161). On the other hand, occlusion of a cerebral artery for surgical convenience raises the problem of ensuring the viability of its territory during the period of occlusion and of estimating the time for which occlusion can be allowed without risk of incurring ischemic damage.

In the case of the middle cerebral artery (MCA), somatosensory evoked potentials (SEP) to contralateral median nerve stimulation at the wrist can conveniently be used to monitor function of the sensory pathway and cortex representing the palm of the hand. The value of SEP monitoring during MCA aneurysm surgery in providing an indication of the time for which the MCA can safely be occluded was investigated in a preliminary series of patients.

Patients and methods

Five patients with a large aneurysms at the bifurcation of the MCA underwent surgery via a pterional, transsylvian approach using microsurgical techniques. There were two males and three females, aged between 39 and 52 years (mean: 45.6 years). all had had at least one episode of subarachnoid hemorrhage, at which time three had shown a transient hemiparesis. Preoperatively, all were in grade I or II according to Hunt and Hess (84). One case underwent surgery three days after subarachnoid hemorrhage; in the other four the interval was 14 days or more.

Surgery was carried out under steroid cover and under moderate hypothermia induced by surface cooling, with lumbar drainage of cerebrospinal fluid after the dura was opened. A pethidine-relaxant anesthetic technique was employed following induction of anesthesia with thiopental. Details of the anesthetic technique are described elsewhere (20). No volatile anesthetic agents were used other than nitrous oxide.

In each case a temporary clip was placed on the distal M1 segment of the MCA about 5 mm proximal to its bifurcation, distal to the origin of the proximal lateral striate arteries, during the final stages of dissection of the aneurysm. It was removed when the aneurysm had been clipped (or wrapped in one case). MCA occlusion times ranged from 8 to 19 minutes (Table 1). Throughout the period of MCA occlusion, the mean systemic arterial blood pressure (MSABP) was kept at a high normal level. Arterial carbon dioxide tension was kept constant with mild hyperventilation. After the aneurysm was clipped, a solution of 5% papaverine was applied locally for 15 minutes.

Sensory cortical function in the territory of the MCA was monitored by recording SEP to contralateral median nerve stimulation at the wrist, using Nicolet CA 1000 equipment and skin contact electrodes situated at the C_3' and C_4' locations according to the international 10-20 system, and over the second cervical spine. A frontal reference electrode was used. Skin contact electrodes were used for stimulation, with the cathode 3 cm proximal to the anode at the wrist. Square waves of 200 μsec duration were delivered at a rate of 5 to 7 per second. An average of 500 responses was taken. Since the cervical recording was technically unsatisfactory in most of these cases, the responses were evaluated by comparing the latencies of the N_{20} peaks recorded from the operated hemisphere with those from the non-operated side under as nearly the same conditions as possible.

Results

The results are summarised in Table 1. The time for which the cortical response

Table 1. N_{20} peak latencies during temporary middle cerebral artery (MCA) occlusion and their recovery times on reperfusion.

Case	Total MCA occlusion time	Temp	Occlusion time	N_{20}peak delay	Occlusion time	N_{20}peak delay	Recovery time
1	19 min	29.0°C	10 min	> 5 msec	17 min	NR	98 min
2	13 min	29.3°C	13 min	none			2 min
3	12.5 min	29.0°C	9 min	> 4 msec	11 min	NR	86 min
4	18 min	30.6°C	8 min	1.8 msec	18 min	> 2 msec	11 min
5	8 min	29.4°C	6 min	NR			≥ 23 min

Temp indicates nasopharyngeal temperature during MCA occlusion
NR indicates no recognisable N_{20} peak.

is well preserved on the side of operation relative to the contralateral, non-operated cortex is very variable. In case 2, the SEP was preserved with about 50% of its pre-ischemic amplitude and an unchanged latency of the N_{20} after 13 minutes of

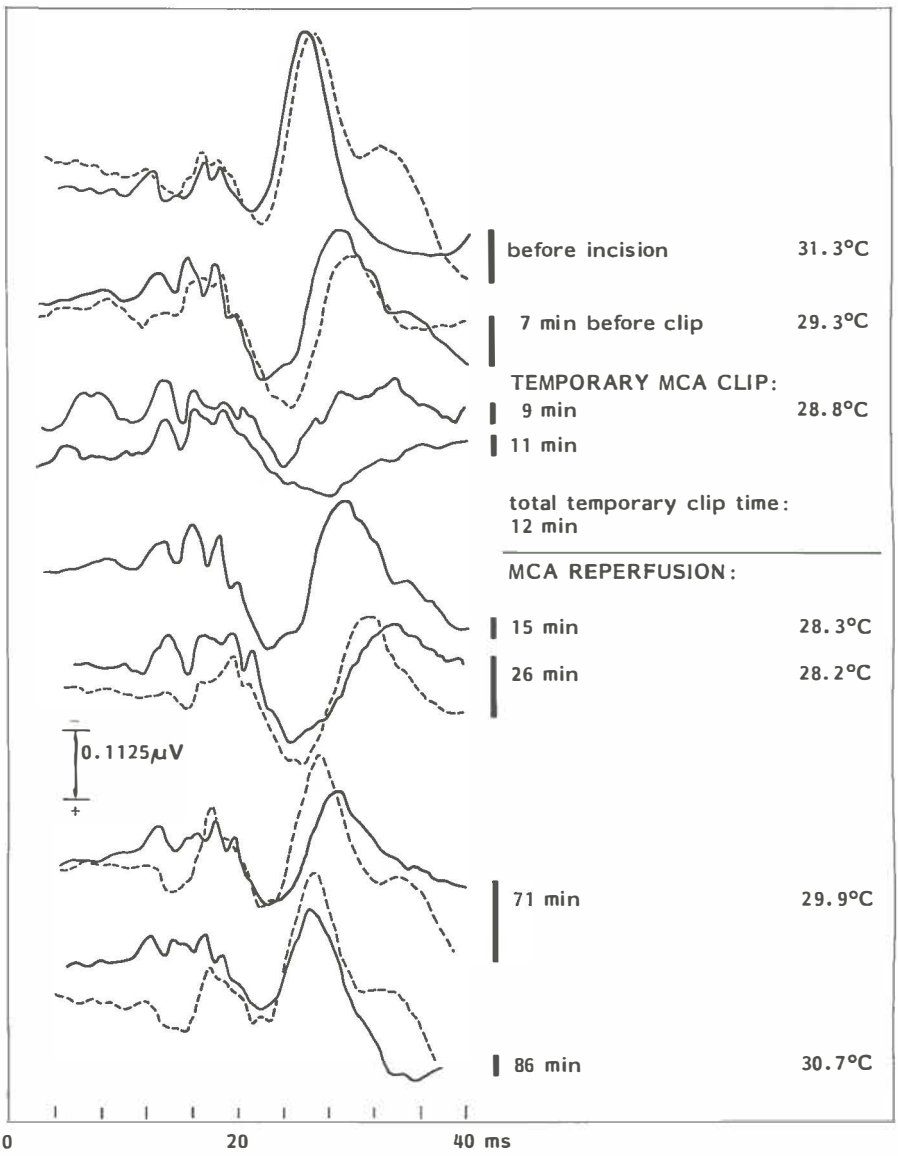

Fig. 1. Case 3. Somatosensory evoked potentials in response to contralateral median nerve stimulation at the wrist, recorded from parietal scalp electrodes during MCA aneurysm surgery before, during and after temporary MCA occlusion. Solid lines: recorded from side of operation. Interrupted lines: recorded from non-operated side. Temperatures to the right of the traces are nasopharyngeal. The N_{20} peak is seen after a latency of about 30 msec at 29.3°C.

MCA occlusion; on reperfusion, the amplitude recovered to greater than the pre-ischemic value within three minutes. Case 4 showed a latency increase of the N_{20} of 1.8 msec after 8 minutes' MCA occlusion and a latency increase of over 2 msec after 18 minutes' occlusion. This was followed by recovery to a response symmetrical with the non-operated hemisphere within 11 minutes of reperfusion.

Two cases (1, 3) showed an increase in latency of more than 4 msec after 9 minutes of MCA occlusion with severely distorted or absent responses after 17 and 11 minutes respectively. The temporary clip was released within three minutes of these times and recovery of the SEP to a response symmetrical with the non-operated side was seen after 89 and 86 minutes respectively. Recordings from case 3 are shown in Figure 1. In case 5, a poor response was seen after 6 minutes of MCA occlusion. Recovery of the response following 8 minutes' occlusion was not complete after 23 minutes but was seen at the end of the surgery.

In no case was the temporary clip in place for longer than 3 minutes in the presence of a markedly distorted cortical SEP. The preservation of the SEP during MCA occlusion did not appear to be clearly related to the prevailing nasopharyngeal temperature. The more severely the SEP was disturbed during the ischemic period, the longer the recovery time; however, there was no obvious relationship between the time taken for recovery and the duration of MCA occlusion. Recovery of the SEP to its pre-ischemic relationship with that of the contralateral hemisphere was seen in all cases before the end of surgery. All patients were awake following rewarming to normal temperatures and none showed any neurological deficit either in the immediate postoperative period or after 6 months.

Discussion

The technique of Hume and Cant (81) of measuring changes in the central conduction time (CCT), i.e., the interval between the arrival of the volley at the dorsal columns (N_{14}) and its arrival at the cerebral cortex (N_{20}), eliminates the contribution of peripheral nerve and spinal conduction times and their variations to latency measurements of the cortical peaks. Although the use of a CCT is undoubtedly preferable, this was not possible in most of these cases for technical reasons. Nevertheless, comparison of the latencies of the N_{20} peaks recorded from the two hemispheres at the same time provided a means of assessing cortical function during temporary MCA occlusion. Conduction in the central multisynaptic pathways is delayed to a greater extent at low temperatures than is peripheral conduction (83, 112) so that reliance must be placed on comparison of the cortical response from the two hemispheres.

The five cases considered here show a wide variation in the preservation of SEP

to contralateral median nerve stimulation at the wrist during MCA occlusion under hypothermia, ranging from a poor response within 6 minutes to no increase in latency after 13 minutes. Up to 19 minutes' occlusion were tolerated at 29.0°C to 30.6°C without evidence of postoperative neurological sequelae. In none of these cases was it felt necessary to interrupt surgery to allow a period of reperfusion on the basis of deterioration of the SEP before completing dissection and clipping the aneurysm. The recovery time for the SEP following reperfusion was also variable, ranging from 2 minutes to 2 hours. It is tempting to assume that these variations reflect variations in residual flow during MCA occlusion. In man, it is known that some individuals survive chronic MCA occlusion without neurological deficit. Carter et al. (42) observed no significant increase in cortical blood flow during temporary occlusion of the MCA in patients undergoing superficial temporal - MCA bypass surgery. Local cerebral blood flow during acute transorbital MCA occlusion in monkeys has been reported as 50% of pre-occlusion values in one study (110) and in another as between 9% and 107% of control flow, with one animal out of 8 showing no neurological deficit (143). Symon has demonstrated some leptomeningeal collateral circulation in the MCA territory during MCA occlusion in the monkey (216). The transorbital occlusion employed in most of the experimental work, however, involves the proximal M1 segment in contrast to the distal occlusion used in these cases, so that their effects cannot strictly be compared.

Suzuki et al. (214) described 152 cases where temporary MCA occlusion was employed without SEP monitoring. These can be seen to fall into four groups. In four cases with upto 20 minutes' MCA occlusion at normothermia there were no permanent sequelae; in 66 cases with upto 40 minutes' occlusion at 27°C, 30 (45%) had no postoperative deficit; in 50 cases with 15 to 30 minutes' occlusion at normothermia with 20% mannitol, 29 (56%) had no deficit, while in 32 cases with less than 15 minutes' occlusion at normothermia with 20% mannitol, 28 (87.5%) had no deficit Transient postoperative deficits were not reported.

Ljunggren et al. (103) used temporary occlusion of the proximal M1 segment of the MCA in 5 cases and of the distal M1 segment in 5 cases with normothermia and without SEP monitoring and concluded that either is well tolerated for upto 20 minutes in early aneurysm surgery.

Symon (219) reported 8 MCA aneurysm cases where temporary MCA occlusion was employed during surgery at normothermia. Of these, one sustained a permanently increased neurological deficit postoperatively after 7½ minutes' occlusion and five cases developed transient deficits after occlusion times ranging from 4 to 40 minutes. In six cases where temporary MCA occlusion was monitored with SEP (223), he concluded that when the CCT does not exceed 10 msec, no permanent neurological deficit is likely to follow. He also described a marked variation in CCT changes between cases during MCA occlusion, some

showing no change and others showing a prolongation of upto 3 msec within 3 minutes. McPherson (124) reported a case of 12 minutes' MCA occlusion at normothermia, necessitated by aneurysmal rupture, where the SEP became unrecordable after 10 minutes. This was followed by a neurological deficit which resolved over 24 hours, at which time the SEP was symmetrical in the two hemispheres.

The difference in outcome between the last two groups of Suzuki, with similar conditions but different occlusion times and the correlation reported between SEP and neurological status in MCA aneurysm patients (124, 54) are suggestive that intraoperative SEP monitoring during temporary MCA occlusion may be useful in assessing permissible occlusion times in individual cases under the particular prevailing conditions of MSABP, anesthetic agents and technique and temperature. At 28°C, used in these cases, cerebral oxygen consumption is approximately one half of that at 37°C (174). At this temperature, permissible cerebrovascular occlusion times can be expected to be approximately doubled (30).

The threshold of cerebral blood flow for synaptic transmission failure where reversible loss of motor function occurs (143, 87) has been demonstrated experimentally to be separated by 5 to 10 ml/100 g/minute from that of membrane failure, which is followed by infarction (11). In the intervening zone of penumbra (10), electrophysiological activity is slowed and finally lost at lower flows, while neuronal viability is preserved and normal function returns if adequate perfusion is restored within a limited period of time. This period becomes shorter the more severe the ischemia (87). Loss of the SEP at flows above the threshold for membrane failure implies a margin of safety when using the SEP as an indicator of focal cerebral ischemia. If prompt action is taken to increase flow when the SEP deteriorates, it should be possible to avoid permanent ischemic damage. Progressive lengthening of the CCT in cerebral aneurysm patients when cerebral blood flow falls below 30 ml/100 g/minute has been elegantly demonstrated by Rosenstein et al. (171).

Nevertheless it should be stressed that certain considerations qualify the validity of SEP monitoring as an indicator of cortical function during the occlusion of a cerebral artery. Only the integrity of the sensory pathway and topographically specific area representing the peripheral distribution of the nerve being stimulated is under scrutiny; information so obtained cannot necessarily be extrapolated to other cortical sensory areas or to the motor cortex, where ischemia would not be detected using the SEP. Although some anastomoses may exist between the leptomeningeal and cortical arteries, as has been shown in the monkey (216), inhomogeneities in cortical perfusion are likely to be accentuated during the occlusion of a major vessel. Part of the territories of the MCA, anterior cerebral, posterior cerebral and basilar arteries can each be monitored by the

responses to median or posterior tibial nerve stimulation, visual evoked potentials or brain stem auditory evoked potentials respectively. In some cases it may be appropriate to monitor more than one modality during cerebrovascular occlusion. Further, of the 402 perforating arteries described by Umansky et al. (229) as arising from the M1 segment of the MCA, a number must arise distal to the temporary clip and these, as well as those with their origin at the bifurcation itself (111), will be perfused by collateral flow when the M1 segment is occluded 5 mm proximal to its termination. Ischemia of subcortical structures supplied by these vessels will not be detected by the SEP if they are not involved in the specific sensory pathway monitored by the SEP. However, the isolated subcortical infarction described by Adams et al. (3) was the result of occlusion of the MCA at or very near its origin, which is not comparable to the occlusion employed in the cases discussed here. In addition, deeper and phylogenetically older parts of the brain are less sensitive to hypoxia than is the neocortex (32).

Regional cerebral oxygen consumption, measured by positron emission tomography (PET), has been found to be more reliable than cerebral blood flow in defining a threshold for neuronal viability in one study (164). However, PET is not yet generally available for intraoperative use. Cortical blood flow has been measured intraoperatively using thermal dilution probes (69) and using intravenous xenon injection (42), but these techniques are costly and cumbersome to perform routinely in the operating room. EEG monitoring has been used during carotid disobliteration surgery (114, 43, 208) and in cardiopulmonary bypass surgery (206) as well as in aneurysm surgery (86) with a variable degree of success. Among its limitations is its inapplicability in the presence of high doses of barbiturates, in contrast to the SEP, which remains a useful indicator of cortical function in the presence of over twice the dose needed to produce a flat EEG (50; case to be reported elsewhere).

In conclusion, our preliminary results indicate that monitoring cortical evoked potentials in response to topographically appropriate peripheral nerve stimulation, perhaps with hypothermia, could make a major contribution to the avoidance of ischemic damage during temporary vascular occlusion in aneurysm surgery. In this way the various benefits of this technique to both surgeon and patient can be realised with minimal risk.

Summary

Somatosensory evoked potentials (SEP) in response to median nerve stimulation were used as a guide to cortical function during temporary occlusion of the distal M1 segment of the middle cerebral artery (MCA) in the surgical treatment of five large aneurysms of the MCA bifurcation. MCA occlusion times ranged from 8 to 19 minutes under moderate hypothermia at 28.8° to 30.3°C. SEP

were preserved for a variable time during MCA occlusion, ranging from no increase in latency after 13 minutes' occlusion to severe deterioration after 6 minutes. In no case was MCA occlusion maintained for longer than 3 minutes in the presence of a severely distorted SEP. Recovery of the SEP to its preoperatively relationship with that of the non-operated hemisphere was seen in all cases before the end of surgery. All patients were awake following rewarming at the end of surgery without any neurological deficit. It is suggested that monitoring SEP pertaining to the territory of a cerebral artery during its temporary occlusion can make a valuable contribution to the avoidance of ischemic damage and will allow the surgeon to take advantage of the several benefits of this technique in aneurysm surgery.

CHAPTER IV.4

Evoked potential monitoring and temporary clipping in cerebral aneurysm surgery

A. Buchthal, M. Belopavlovic, J. J. A. Mooij.

Acta Neurochirurgica, in press.

Introduction

For many years a greater or lesser degree of systemic arterial hypotension has been in widespread use to facilitate the dissection of intracranial aneurysms. This, however, carries its own morbidity (156) and can result in regional cerebral hypoperfusion in patients who have suffered subarachnoid haemorrhage (SAH) as a result of failure of autoregulation of cerebral blood flow in the affected areas (52, 217). Further, intraoperative aneurysm rupture can occur in spite of arterial hypotension: this is frequently followed by severe and persistent vasospasm which can lead to cerebral ischaemia and oedema with devastating consequences (16, 62). Elective temporary occlusion of the parent artery of an aneurysm is now being increasingly employed as an alternative to arterial hypotension (85, 93, 103, 214, 219). This produces partial or total collapse of the aneurysm and reduces the risk of rupture to a minimum.

If a cerebral artery is to be occluded for surgical convenience, however, the viability and function of those areas subjected to ischaemia during the occlusion must be guaranteed. The somatosensory evoked potential (SEP) has been shown to be useful as an indicator of developing ischaemia in SAH patients (221) as well as for intraoperative monitoring (223). The basis for the use of the SEP for this purpose is provided by experimental work which has established several thresholds of cerebral blood flow. The SEP is unaffected at a local cerebral blood flow (lCBF) above 20 ml/100 g/minute. At lower flows it declines sharply and electrical silence occurs by the time about 15 ml/100 g/minute is reached. This is the threshold for synaptic transmission failure (35). Neuronal membrane failure occurs at lower flows of 8 to 10 ml/100 g/minute, with massive release of intracellular potassium followed by infarction (11, 33). Between these two flow thresholds there is a range of cerebral blood flow where neurones no longer function but retain the capacity for full functional recovery. This becomes time limited, severer degrees of ischaemia being tolerated for progressively shorter periods of time (87). A zone with perfusion in this range typically surrounds the

central area of infarction in focal ischaemia and is known as the ischaemic penumbra (10, 220). Its existence implies that the SEP should have the capacity to serve as an early warning of a critical degree of ischaemia during the temporary occlusion of a cerebral artery. In a pilot series of six middle cerebral artery (MCA) aneurysm cases the technique promised to be of practical application (141). The value of the SEP in providing an indication of safe cerebrovascular occlusion time during moderate hypothermia was assessed in 25 cases.

Methods

SEP monitoring was carried out in 25 cases where temporary arterial occlusion was employed. All except one case were in Hunt and Hess's grade I or II (84) preoperatively. Two MCA cases underwent early surgery and five aneurysms were unruptured.

Surgery

Surgery was carried out under dexamethasone cover and via a pterional, transsylvian approach using microsurgical techniques and lumbar cerebrospinal fluid drainage as described previously (141). In 13 of the 15 MCA cases, the M1 segment of the MCA was occluded distally, about 5 mm proximal to its termination and distal to the proximal lateral striate arteries; a more proximal occlusion was employed in two cases. Bilateral occlusion af the A_1 segment of the anterior cerebral artery (ACA) was employed in five aneurysms of the anterior communicating artery (ACoA) complex. The internal carotid artery (ICA) was occluded intracranially or in the neck in five cases.

Anaesthesia

Anaesthesia was induced with sodium thiopentone and suxamethonium chloride and maintained with pethidine, pancuronium and ventilation with 33% oxygen and 66% nitrous oxide. Moderate hypothermia was induced by surface cooling following premedication with a lytic cocktail. Sodium nitroprusside was used to control the arterial blood pressure (SABP) as needed. During the arterial occlusion the SABP was raised to a high normal level. Arterial carbon dioxide tension (P_aCO_2) was kept constant at 4.0 to 4.5 kP. Volatile anaesthetic agents other than nitrous oxide were not used. Nasopharyngeal, oesophageal and skin temperatures were monitored.

Two cases were ventilated with 100% oxygen starting a short time before the arterial occlusion and given barbiturates to ensure an adequate depth of anaesthesia during that time. One case with two MCA aneurysms was loaded prophylactically with 44 mg/kg pentobarbitone, as described previously (20).

SEP monitoring and evaluation

(i) In the MCA and ICA occlusion cases, SEP's in response to contralateral median nerve stimulation at the wrist (MN-SEP) were monitored. Skin contact electrodes were used in earlier cases and platinum needle electrodes in later cases, placed at C_3' and C_4' (American EEG Society) and over the cervical spine for recording. A frontal reference was used in earlier cases and a linked ear reference in later cases. Square waves of 200 μsec duration were delivered via skin contact stimulating electrodes at a rate of 5 to 7 per second and with an intensity of 12 to 15 mA. 500 responses were averaged whenever possible using Nicolet CA 1000 equipment. During the period of vascular occlusion, however, 100 - 200 usually had to be accepted in order to update the monitoring as rapidly as possible. This was usually possible within a two minute interval. Evaluation of the responses was based on the technique of Hume and Cant (81), using the central conduction time (CCT) whenever possible to compare the responses of the two hemispheres and to evaluate sequential changes in one hemisphere. As illustrated in Figure 2, Chapter IV.2, the CCT is the time interval between the peak recorded over the cervical spine and the first negative cortical peak (N_{20}). Use of the CCT eliminates the contribution of variations or differences in peripheral conduction velocity to the measurement of the latency of the cortical response. During the period of occlusion only N_{20} peak latencies were measured in rapid succession, due to the restricted number of memories of the apparatus. Temperatures were generally quite stable at this time and any changes were taken into account. The cortical evoked response was considered to be absent when a wave of less than 10% of the previous amplitude of the N_{20} was seen on visual inspection within the time base of 40 msec, in the presence of persisting cervical and/or subcortical responses, and in the absence of exessive interference in the incoming signal. An apparently absent response was confirmed by repeated recordings. In the first five MCA cases where surface electrodes were used, the cervical peak was not recorded satisfactorily and the N_{20} peak had to be used for evaluation throughout in the two hemispheres (see Chapter IV.3).

(ii) In the five cases where the A_1 segment of the ACA was occluded, SEP's in response to contralateral stimulation of the posterior tibial nerve (PTN-SEP) were monitored. An active electrode at C_z' was used with a linked ear reference. Stimulation rates of 2 to 3.7/sec were used and 500 responses were averaged whenever possible. Since A_1 occlusion was bilateral, the potentials could be evaluated during the period of occlusion only on the basis of acute, sequential changes in N_{70} latency in one hemisphere. For this purpose, the hemisphere whose A_1 and A_2 supply was most closely associated with the aneurysm was selected. This was necessitated by the slower stimulation rates; faster rates did not yield a satisfactory recordings. Evaluation was in other respects as described in (i) above.

Results

The 25 cases involved temporary occlusion of the vessels indicated in Table 1.

Table 1. 25 cases temporary occlusion.

SEP		artery	occlusion site
MN	13	MCA	distal M1
	2	MCA	proximal M1
	5	ICA	
PTN	5	ACA	bilateral A_1

MCA = middle cerebral artery
ACA = anterior cerebral artery
MN = median nerve
PTN = posterior tibial nerve
SEP = somatosensory evoked potential
ICA = internal carotid artery

I. MCA occlusion cases

MCA occlusion times ranged from 6.3 to 52 minutes at 28.6°C to 31.3°C.

(i) Persistence of MN-SEP during MCA occlusion.

The MN-SEP was lost within 5 or 6 minutes of MCA occlusion in three cases: of these, two were early interventions, of which one had shown a transient neurological deficit at SAH, and the third had marked vasospasm during surgery and had a proximal M1 occlusion. Three cases lost the response after 9 to 17 minutes of MCA occlusion (Table 2). Case 4, who had an aphasia and a dense

Table 2. Loss of SEP in MCA occlusion.

Case	SEP lost	Comments
1	5 min	Early surgery
2	6	Severe vasospasm
	5	Prox. M1 occlusion
3	6	Early surgery Deficit at SAH
4	9	H&H III; extensive deficit at SAH; no back flow
5	11 min	Deficit at SAH
6	13	Slight deficit at SAH Prox. M1 occlusion
7	17	—

hemiplegia at the time of SAH with a residual dysphasia preoperatively and where the absence of back flow was noted during the occlusion, lost the MN-SEP within 9 minutes. Cases 5 and 6 both had had neurological deficits at the time of

SAH and case 6 had a proximal M1 occlusion. Intraoperative records from case 4 are shown in Figure 1.

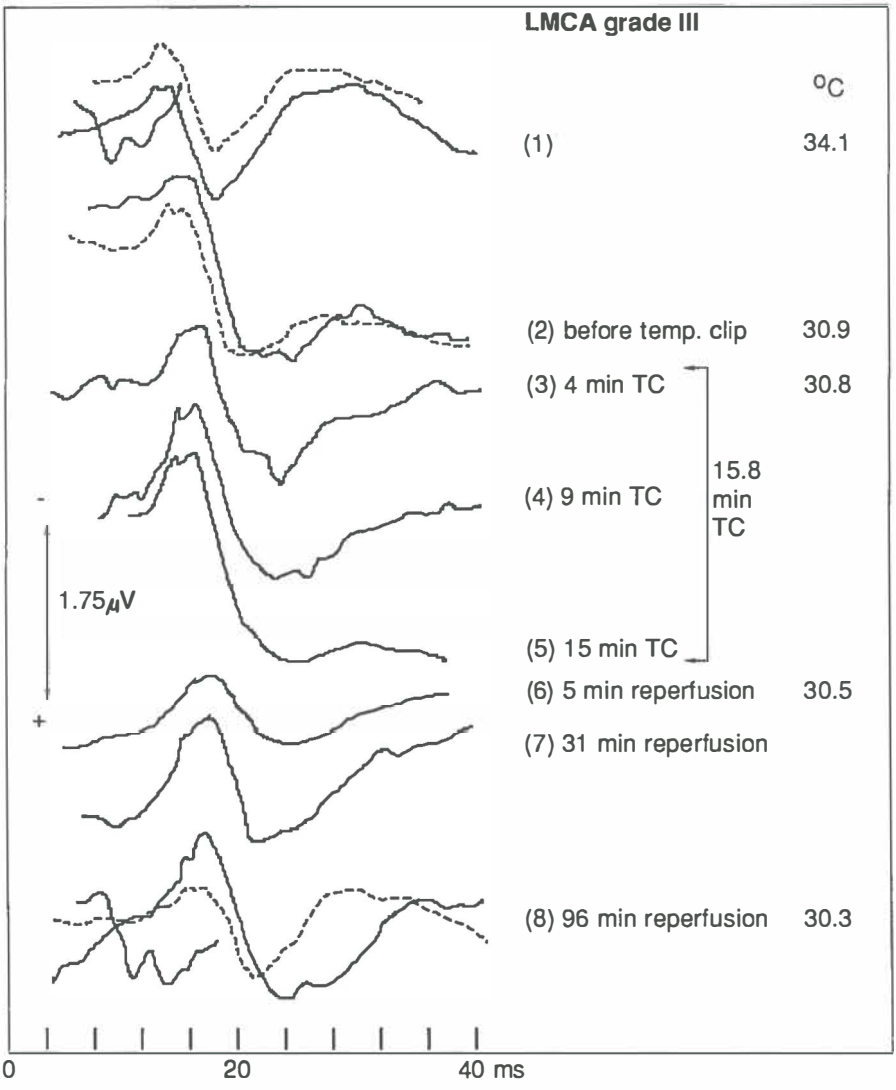

Fig. 1. Intraoperative somatosensory evoked potential (SEP) records in MCA case 4. Solid lines were recorded over the cervical spine and left cerebral cortex after stimulation of the right median nerve; interrupted lines were recorded over the right cortex. SEP are recorded negative upwards. Temperatures are nasopharyngeal. TC = temporary clip on LMCA. There is no clear N_{20} peak after 9 minutes' TC (record 4). 96 minutes after removing the TC the central conduction time (CCT) is prolonged in the left hemisphere by over 6 msec with respect to the right. There was an increased neurological deficit postoperatively.

In the remaining 8 cases the MN-SEP persisted throughout occlusion periods of 6.3 to 52 minutes (Table 3). Small prolongations in CCT were seen in two unruptured aneurysm cases while no prolongation was seen in four cases after 6.3

Table 3. 8 MCA occlusion cases: SEP preserved.

Case	Occlusion time	CCT prolong.	Comments
9	18 min	2ms	some back flow
10	19.1	0.9ms	—
11	9 11.8 3	1.2ms 0.6ms	unruptured
12	18.4	0.52ms	unruptured
8	13 min	none	—
14	6.3	none	100% $/_2$
15	28 29	none	44 mg/kg PB
13	16 52	none	good back flow

to 52 minutes of MCA occlusion. The last group includes one case given 100% oxygen prior to occlusion because a long occlusion time was anticipated in view of technical problems and the case given a pentobarbitone load. Records from the pentobarbitone case are shown in Figure 3, Chapter IV.2, p. 71.

(ii) Duration of occlusion after loss of the MN-SEP and neurological complications.

Neurological complications were seen postoperatively in three cases. Case 4 had an increased deficit with extension of the pre-existing infarct after MCA occlusion had continued for 7 minutes in the absence of an SEP. Her neurological condition improved markedly over the nex two months. In one case subjected to early surgery where the occlusion continued for four minutes after loss of the MN-SEP, there was a mild deficit which resolved over two weeks. In the third case, where the MN-SEP was absent for two periods of 4 and 11 minutes, there was a postoperative weakness which resolved within 24 hours. Two minutes of

Table 4. MCA occlusion, loss of SEP and outcome.

Case	Total MCA occlusion time	SEP lost	SEP absent	Postoperative complications
1*	8.5 min	5 min	4 min	Transient new deficit, 2 weeks
2	10 min 16 min	6 min 5 min	4 min 11 min	Transient new deficit, 24 hours
4**	15.8 min	9 min	7 min	Increased deficit
3*, 5, 6, 7	8-19 min	6-17 min	2 min	None

* Early surgery

** Hunt & Hess grade III + infarct

MCA occlusion after loss of the SEP were tolerated by four cases without neurological sequelae; three of these had had deficits at the time of SAH. The relationship between the duration of MCA occlusion after loss of the MN-SEP and neurological outcome is summarised in Table 4. There were no complications in the cases where the SEP persisted throughout the occlusion.

II. ICA occlusion cases

The five ICA occlusion cases are summarised in Table 5. ICA occlusion times ranged from 5.5 to 22 minutes at 30.2°C to 32.5°C.

The MN-SEP was lost in one case after 7 minutes' ICA occlusion where the absence of back flow was noted; reperfusion was instituted one minute later and the patient had a paresis postoperatively which responded to intravascular volume therapy and resolved within four hours. No major SEP changes were seen in the other four cases and there were no other complications.

Table 5. Five ICA occlusion cases.

Case	Occlusion time	MN-SEP: CCT	Sequelae
1	7 min	absent	4 hrs paresis
4	22	0.64ms prolong.	—
5*	8	0.1ms prolong.	—
2	5.5	no change	—
3	5.5 4.1	no change	—

* 100% O_2 during occlusion.
CCT = central conduction time.

III. Bilateral A_1 occlusion.

Five cases where bilateral A_1 occlusion was employed are summarised in Table 6. Occlusion times ranged from 13.8 to 45 minutes at 29.8°C to 31.5°C. A poor PTN-SEP was seen in one case after 16 minutes of bilateral occlusion; reperfusion was established one minute later. One case showed a 6 msec delay in the N_{70} peak latency after 16 minutes' bilateral and 32 minutes' right A_1 occlusion while two

Table 6. Five bilateral A_1 occlusion cases.

Case	PTN-SEP	at occlusion time
1	absent	16 min
2*	6ms N_{70} delay	16 min bilat + 32 min R.
3	1.44ms	20 min
4	no change	42 + 17 min
5*	no change	13.8 + 7.0 + 5.75 min

No neurological sequelae.
* Unruptured aneurysms.
PTN-SEP = evoked potential to posterior tibial nerve stimulation.

cases showed no changes after two periods of 42 and 17 minutes in one case and three periods of 13.8, 7 and 5.75 minutes in the other. There were no neurological complications in this group.

Discussion

The use of the SEP as a monitor of brain ischaemia during the occlusion of a cerebral artery requires that the cortical area or pathway being monitored will be maximally affected by the ischaemia resulting from the occlusion. The modility or modalities to be monitored must therefore be carefully chosen in order to achieve this. In the case of the MCA, the sensory cortex representing the palm of the hand can conveniently be monitored by means of the SEP in response to stimulation of the contralateral median nerve at the wrist, together with the intervening pathway. The ACA supplies the cortex representing the feet and can be monitored using the response to posterior tibial nerve stimulation at the ankle, while visual evoked potentials and the MN-SEP together cover the territory of the posterior cerebral artery, which supplies the calcarine cortex and the thalamus.

It must nevertheless be borne in mind that any one SEP modality provides information pertaining exclusively to that specific pathway, from stimulus and sense organ to cortex, while the state of the sensory pathways and cortical areas, the motor cortex and subcortical structures supplied by perforating vessels can only be inferred on the basis of uniform perfusion and sensitivity to ischaemia throughout the ischaemic area. However, inhomogeneities of perfusion within the territory of a cerebral artery cannot be ruled out and may be accentuated during occlusion of that artery in the presence of vascular pathology, such as a spastic or stenotic segment. Even severe local ischaemia cannot be detected if the monitored pathway is not significantly affected. This must be regarded as one limitation of the technique.

In all except two of the 15 MCA cases the M1 segment was occluded distally, in contrast to the proximal, transorbital occlusion usually employed experimentally. It is nevertheless inevitable that some of the 402 perforating branches described by Umansky et al. (229) as arising from the M1 segment will be perfused only by back flow during the occlusion period. Branston et al. (32) found that the neocortex was the most sensitive to ischaemia during MCA occlusion in baboons, phylogenetically older sructures having lower flow thresholds. On the other hand, there is some evidence in cats that in global ischaemia, subcortical white matter suffers the severest ischaemia, resulting in a condition block to the cortex while the latter is relatively well perfused (99).

The following discussion concerns primarily the MCA occlusion cases since they form the largest group and include three cases which approached the limits of tolerance to ischaemia.

The wide variation in MCA occlusion time before the MN-SEP was lost or affected must be at least partly related to correspondingly large variations in back flow or collateral perfusion. This can be assessed crudely by visual inspection and corresponds to the severity of ischaemia. Our observations suggest that in SAH patients another major factor determining tolerance to an ischaemic insult is pre-existing local ischaemia, with or without neuronal damage or infarction, present immediately preoperatively or occurring transiently at the time of SAH. This manifests itself in either case as a neurological deficit and is reflected in the rapidity and extent of SEP changes during the occlusion. It has been demonstrated in the baboon that repeated episodes of cerebral ischaemia render the brain more sensitive to further episodes (199). In this context, SAH itself must be regarded as an ischaemic insult whose severity is indicated by any neurological deficit at that time. A period of vascular occlusion during early surgery, i.e., within 48-72 hours of SAH, can therefore be expected to be less well tolerated than a similar period in late surgery. The two MCA cases subjected to early surgery illustrate this, losing the MN-SEP within 5 and 6 minutes of MCA occlusion. A third case lost the SEP after a similar time in the presence of marked vasospasm. In contrast, occlusion of parent arteries of unruptured aneurysms was well tolerated, only small prolongations in CCT being seen in two MCA cases after 18.8 and over 20 minutes' occlusion. Bilateral A_1 occlusion was also well tolerated for 16 and 14 minutes in two cases.

Three MCA occlusion cases approached the limits of tolerance to focal ischaemia under the prevailing conditions. A transient paresis was seen in one case where MCA occlusion was maintained for two periods of 4 and 11 minutes after loss of the MN-SEP. A mild, transient deficit followed MCA occlusion for 4 minutes after loss of the SEP in a second and in the third, seven minutes of continued MCA occlusion after loss of the SEP in a patient with pre-existing infarction in the territory of the MCA was followed by an increased deficit and extension of infarction. However, two minutes of MCA occlusion after loss of the SEP were tolerated by four cases without neurological sequelae.

Systemic arterial hypotension has been demonstrated in the monkey to lead to extension of pre-existing infarction (126, 167). The same will apply to focal ischaemia of an area containing infarcted tissue, where autoregulation is defective. This suggests that patients at high risk from ischaemic damage during temporary vascular occlusion are also likely to tolerate systemic hypotension badly. Surgery without the use of temporary occlusion cannot be recommended for these patients, which include those with preoperative focal neurological deficits, those undergoing early surgery and those who had a deficit at the time of SAH, since the use of some degree of arterial hypotension is inevitable if vascular occlusion is not employed. Moreover, intraoperative rupture again becomes a real possibility. It is perhaps not remarkable that the factors associated with poor

tolerance of temporary vascular occlusion in the cases discussed here are factors recognised to carry an increased risk in aneurysm surgery in general. The operative risk for these patients can perhaps be reduced by the use of one or more measures designed to increase tolerance to focal or global ischaemia, together with temporary vascular occlusion and appropriate SEP monitoring. Deterioration or loss of the SEP could then be used as an indication for reperfusion of the vessel followed by a further period of occlusion with or without the employment of one or more of these measures.

The first of these measures is to raise the arterial blood pressure, which maximises collateral perfusion during vascular occlusion because this is pressure dependent. The second measure is to reduce oxygen demand. Moderate hypothermia was used in all the cases discussed here. At 28°C, cerebral oxygen consumption is approximately one half of that at 37°C (174). The relatively long occlusion times we have used compared to those which can be safely used at normothermia (85, 93, 103, 214, 219) with a low morbidity are undoubtedly attributable to the use of hypothermia. Hypothermia has been used successfully with temporary vascular occlusion in the past (30, 108), before being generally abandoned by neurosurgeons in the mid-1960's.

Tolerance to focal ischaemia can also be increased by the use of barbiturates. Large doses of barbiturates were effective in ameliorating the effects of experimental focal ischaemia in primates when this was of limited duration and therapy was started early (184, 185). Temporary vascular occlusion during surgery should provide suitable conditions for their prophylactic use. Hoff et al. (74) obtained good results with pentobarbitone and moderate hypothermia in two cases where the MCA was occluded for 27 and 90 minutes. The records shown in Figure 3, p. 71 illustrate the practical feasibility of SEP monitoring during MCA occlusion while the EEG is flattened by 44 mg/kg pentobarbitone. No prolongation in the CCT was seen during either of two periods of 28 and 29 minutes of occlusion and there were no complications.

Ventilation with 100% oxygen increases oxygen supply by a small amount which can become significant in critical conditions. In experimental MCA occlusion in baboons, as the lCBF falls to 16 ml/100 g/minute, changing the ventilating gas from oxygen to air markedly depresses the SEP (34). The authors postulated that the reverse effect might be applicable clinically; at low temperatures, where the solubility of oxygen is greater, this will be more pronounced. At these critical levels of lCBF, other factors which normally play a minor role may also reach significance. These include p_aCO_2 (145) and the avoidance of hyperglycaemia (113, 58). Hypertonic mannitol has also been reported to increase tolerance to cerebrovascular occlusion (213), while the use of perfluorocarbons and free radical scavengers offer possibilities for the future (210).

The 15 MCA occlusion cases discussed here indicate that the MN-SEP exhibits a sensitivity to ischaemia in the territory of the MCA which is appropriate for clinical monitoring in the conditions in which we have employed it, i.e., moderate hypothermia, pethidine-relaxant anaesthesia and distal M1 occlusion. The MN-SEP provided a warning of ischaemia which was sufficiently early to allow timely reperfusion when this was necessary.

Kidooka et al. (93) regarded a prolongation of 1.2 msec in the CCT as critical, a longer CCT during MCA occlusion being associated with a new or increased deficit in 8 out of 13 cases. Symon et al. (223) concluded from their experiences that neurological sequelae were likely if the CCT exceeded 10 msec (the average CCT under stable anaesthesia was 6.7 ± 0.7 msec). In both series, surgery was at normothermia. In contrast, our cases tolerated at least 2 minutes of MCA occlusion at 29°C after loss of the MN-SEP without neurological sequelae and a new deficit was not seen without loss of the SEP during MCA occlusion.

It is concluded that appropriate SEP monitoring has the capacity to make a major contribution to patient safety in aneurysm surgery with temporary occlusion of the parent artery, and that moderate hypothermia warrants serious reappraisal for use in this situation.

Summary

Temporary occlusion of the parent artery greatly facilitates the dissection of large cerebral aneurysms, while much reducing the risk of intraoperative rupture and avoiding the use of profound arterial hypotension. Intraoperative somatosensory evoked potential (SEP) monitoring was carried out in 25 aneurysm cases where temporary clipping was employed electively under moderate hypothermia. Occlusion times ranged from 6.3 to 52 minutes at 28.7°C to 32.5°C. Among 15 middle cerebral artery (MCA) occlusion cases the SEP was lost within 5 or 6 minutes in two cases undergoing early surgery and in one case with marked vasospasm and was lost within 9 minutes in one case with pre-existing infarction in the territory of the MCA. The SEP persisted throughout MCA occlusion periods of 6.3 to 52 minutes in 8 cases. Occlusion of parent arteries of unruptured aneurysms was well tolerated. At least 2 minutes of MCA occlusion after loss of the SEP were tolerated without neurological sequelae, while transient new deficits were seen when MCA occlusion was continued for 4 and for 4+ 11 minutes and an increased deficit was seen when occlusion was continued for 7 minutes after loss of the SEP. In each of the internal carotid artery (ICA) occlusion and bilateral anterior cerebral artery occlusion groups the SEP was lost in one case and was absent for about one minute before reperfusion was instituted. The ICA case had a transient deficit lasting about 4 hours; no other complications were seen in these two groups. Complications were not seen in any

case where the SEP was not lost during the occlusion period. Factors affecting collateral perfusion and possible means of increasing tolerance to ischaemia in this situation are discussed. It is concluded that: 1. appropriate SEP monitoring is of value in avoiding sequelae to temporary cerebral arterial occlusion; 2. patients at high risk from ischaemic damage during temporary occlusion include those subjected to early surgery, those in Hunt and Hess' grade III and those who had a neurological deficit at the time of subarachnoid haemorrhage; and 3. hypothermia allows longer occlusion times than at normothermia with a low morbidity and deserves reappraisal for use in this situation.

CHAPTER V

Comment & conclusions

This thesis describes the developments in the operative management of cerebral aneurysm patients in the Neurological Clinic of the Academisch Ziekenhuis, Groningen, over the ten year period, 1977 to 1987. There have been advances in surgical techniques during this period which have been accompanied by a reduction in overall mortality and morbidity. There has also been a change in the approach to the problem of timing of operative intervention, early intervention being increasingly favoured in most centres today so that ruptured intracranial aneurysms are treated as a surgical emergency.

The following conclusions have been drawn from our work:

1. Moderate hypothermia, which has been used traditionally in this Clinic for cerebrovascular surgery and was employed throughout the clinical work described here, has proved itself during this period to be invaluable in cerebral aneurysm surgery. While the first case report illustrates cerebral protection obtained with moderate hypothermia in a cardiac arrest situation (i.e., global ischaemia), the last paper (Chapter IV.4) illustrates its value during the temporary occlusion of a cerebral artery (focal ischaemia).
2. Ischaemic cerebral oedema formation can be successfully combated with very large doses of barbiturates.
3. When cerebral aneurysm patients are given prophylactically a pentobarbitone infusion titrated to maintain a flat EEG, middle cerebral artery aneurysm cases are seen to benefit most, their mortality and permanent morbidity falling from 5/8 to 0/8. Some benefit may be seen in aneurysms of the internal carotid bifurcation, while aneurysms of the anterior communicating artery complex and internal carotid/posterior communicating artery appear to benefit little. This demonstrates barbiturate protection from focal cerebral ischaemia in human beings.
4. This protective effect is independent of the well known effects of barbiturates in reducing cerebral oedema.
5. Barbiturates offered no protection when focal ischaemia was permanent and complete or in global cerebral ischaemia.
6. Pentobarbitone is the barbiturate of choice for clinical use, since it is associated with great haemodynamic stability and minimal lowering of the arterial blood pressure.
7. The dosage of pentobarbitone must be titrated on the basis of depression of cerebral function. The Cerebral Function Monitor is well suited to this purpose. The EEG should be rendered flat rather than allowed to remain at a burst-suppression pattern.

8. The duration of barbiturate therapy should be parallel the time course of the ischaemic insult from which cerebral protection is sought. Premature withdrawal can result in severe rebound cerebral oedema, as illustrated in Case 1 in Chapter IV.2.
9. A flat or isoelectric EEG under the influence of barbiturates does not represent a state of maximal functional neuronal depression. Somatosensory evoked potentials, as well as a cortical electrical response to surgical retraction, persist in the presence of much higher doses than are required to abolish spontaneous cortical activity (i.e., flatten the EEG).
10. Our clinical results are consistent with the contention that maximal cerebral protection in focal ischaemia is obtained in man when substantially higher doses are used than are needed to flatten the EEG.
11. In the presence of very large doses of barbiturates, the EEG is no longer useful as an indicator of cerebral function. Evoked potential monitoring of pathways involving specifically those areas under threat from ischaemic damage should be carried out and has the potential to supply useful information. If the ischaemic areas are not involved in the monitored pathway, such monitoring can have no value.
12. Systemic arterial hypotension not only predisposes subarachnoid haemorrhage patients to regional cerebral hypoperfusion as a result of disturbed autoregulation but also deprives the same areas of any protection which might otherwise have been afforded by hypothermia. In contrast, profound local hypotension can be achieved by the temporary occlusion of the parent or feeding artery of the aneurysm. This technique maintains adequate perfusion to the remaining parts of the brain and the rest of the body, greatly facilitates surgical dissection by promoting partial or total collapse of the aneurysm and almost eliminates the risk of intraoperative aneurysmal rupture. This potentially catastrophic event is justifiably feared by neurosurgeon and neuroanaesthetist alike. Temporary occlusion of a cerebral artery, however, calls for effective monitoring of the ischaemic area(s) so that avoiding action can be taken before irreversible damage occurs. When the middle cerebral artery is temporarily occluded during the dissection of a middle cerebral artery aneurysm, monitoring of the median nerve evoked potential (MN-SEP) provides a reliable indication of the ischaemia suffered by the cortical area representing the palm of the hand. At about 29°C, 2 minutes of occlusion are tolerated after loss of the MN-SEP without detectable neurological deficit.
13. The MN-SEP is lost early during middle cerebral artery occlusion in: (i) cases undergoing early surgery; (ii) cases with a focal neurological deficit immediately preoperatively (Hunt & Hess grade III or more); and relatively early in cases where the has been a transient focal deficit at the time of subarachnoidal haemorrhage. The cases can be identified as high risk groups.

14. Upon loss of the SEP during temporary vascular occlusion, reperfusion of that vessel (by removal of the clip) is desirable. Following this, the clip can be re-applied to allow completion of the dissection. If it is apparent that more than a few minutes of occlusion are likely to be required for this, then the employment of some additional techniques of cerebral protection should be considered, e.g. barbiturate loading before re-occluding the vessel, the use of the Sendai cocktail or of fluorocarbons.
15. Very much longer cerebral arterial occlusion times are permissible without occurring neurological sequelae at a body temperature of about 29°C combined with appropriate SEP monitoring than can be tolerated at normal temperatures.
16. During temporary vascular occlusion, meticulous attention should be paid to the maintenance of a high arterial blood pressure, a normal to high arterial carbon dioxide tension and a low blood glucose level, as indicated in the Discussion of Chapter IV.4.
17. The posterior tibial nerve evoked potential can be used in a similar manner to the MN-SEP when one or both A_1 segments of the anterior cerebral artery are occluded temporarily during surgery of aneurysms of the anterior communicating artery complex.

Summary

Subarachnoid haemorrhage has an incidence of 8.7 per 100,000 population per annum in the Netherlands. Of the intracranial aneurysm cases presenting for surgery at the Neurosurgical Clinic at the Academisch Ziekenhuis, Groningen between 1977 and 1987, about 33% were under the age of 40, 62.5% were under the age of 50 and 90% were under the age of 60 years. Approximately one third of all patients with aneurysmal subarachnoid haemorrhage die or are neurologically disabled following the initial haemorrhage, while recurrent haemorrhage occurs within the next two weeks in 20 % of the survivors. Recent advances in surgical techniques have contributed to bringing the operative mortality down to as little as 2% in many centres. However, a substantial proportion of mortality and morbidity among cerebral aneurysm patients is associated with the development of delayed ischaemic complications resulting from cerebral vasospasm. This may begin to manifest itself from the fourth day post-subarachnoid haemorrhage or be provoked or exacerbated by surgical manipulation. This is particularly the case following intraoperative aneurysmal rupture. Vasospasm can persist for as long as four weeks and may be severe. In the absence of permanent damage resulting form cerebral ischaemia or intracranial hypertension secondary to massive cerebral oedema, however, a good recovery can be anticipated after its subsidence and repair of the aneurysm.

While next to no progress has been made upto the time of writing in combating established cerebral vasospasm, this thesis describes the development over the ten year period, 1977 to 1987, in the Neurosurgical Clinic of the Academisch Ziekenhuis, Groningen, of techniques which can be employed to increase the resistance of the brain to an ischaemic insult during surgery, and of a technique which reduces the risk of intraoperative rupture to a minimum. Broadly, the measures which can be employed intraoperatively to increase tolerance to ischaemia take three forms.

I. Hypothermia. When body temperature is reduced by 9°C, cerebral oxygen consumption falls to about one half of that at normal temperatures. Induced hypothermia was used widely for intracranial aneurysm surgery in the 1960's but is used in very few Neurosurgical centres today. One of the centres where it has remained in routine use for cerebrovascular surgery is the Neurosurgical Clinic of the Academisch Ziekenhuis, Groningen. It has been employed for aneurysm surgery throughout the period under consideration and in all the clinical work described here. Its value is illustrated by the survival after more than 35 minutes' cardiac arrest at 28°C of one case with little ultimate neurological damage. It has also allowed the development of a technique of temporary vascular occlusion which could only be employed in a much more limited form at normal

temperatures. Renewed interest in induced hypothermia for cerebral aneurysm surgery is therefore anticipated in years to come.

II. Barbiturates. This group of drugs has long been known to be effective in reducing cerebral oedema and the intracranial hypertension it causes. Experimental evidence in primates and in non-primates is reviewed and indicates that they are effective in ameliorating the effects of focal cerebral ischaemia when this is of limited duration and the administration of barbiturates is started within a short time after the onset of the ischaemic insult. This effect is dose related and is seen in the absence of cerebral oedema.

Following the satisfactory recovery of a case of fulminating postoperative cerebral oedema after the permanent occlusion of an anterior cerebral artery after treatment with 32 g sodium thiopentone, and in view of an incidence of postoperative complications which we found excessive and of the experimental evidence mentioned above, a series of 33 consecutive cases were given prophylactic barbiturates. The use of sodium thiopentone was associated with disturbances in cardiac rhythm during hypothermia in several cases and, when given as a single loading dose before cooling, its effect was too short lived to cover the period of dissection of the aneurysm. In contrast, pentobarbitone was always associated with haemodynamic stability and no cardiac rhythm disturbances were seen during hypothermia so that its administration could be continued until the aneurysm was clipped.

The clinical results of these cases constitute the first demonstration of cerebral protection by barbiturates in man. This is distinct from their action in relieving intracranial hypertension by reducing cerebral oedema and is entirely consistent with experimental observations in primates. Whereas the combined mortality and permanent morbidity in middle ceerbral artery aneurysm cases was reduced form 5/8 to 0/8, little benefit was seen in internal carotid/posterior communicating artery aneurysm cases or in aneurysm of the anterior communicating artery complex. Although statistically not significant due to the small number of cases, the best results were seen in patients who received the largest doses (upto 57 mg/kg) and the least satisfactory results in patients who received the smallest doses. Withdrawal of barbiturates in the presence of vasospasm resulted in a rebound cerebral oedema which was sometimes severe.

III. Neuromonitoring. The controversial question of the dosage of barbiturates which is appropriate for clinical purposes was investigated by examination of the Cerebral Function Monitor (CFM) recordings of cases which had received prophylactic barbiturates. CFM traces were flat during dissection of the aneurysm in 24 pentobarbitone cases. Serum pentobarbitone levels were not consistently related to spontaneous cortical electrical activity either during pentobarbitone administration or during recovery either in a single patient at different times or in different patients with similar levels of cerebral activity. In

the presence of a flat CFM trace, a response to surgical stimulation persisted in all cases, sometimes accompanied by acute hypertension.

The complications of these findings are discussed. Larger doses of pentobarbitone than are needed to flatten the EEG were well tolerated by all patients at 29°C. When spontaneous electrical activity is abolished by barbiturates this evidently does not represent a state of maximal functional neuronal depression: a response to retraction persists, as do various modalities of evoked potential. The evoked potential is therefore suitable for monitoring cerebral function when the EEG is rendered flat by barbiturates: indeed, there is no alternative means of assessment in this situation.

Further, since the protective effect of barbiturates is decsribed as being dose related, extending to doses far in excess of those needed to flatten the EEG, and functional neuronal depression is far from maximal when the EEG is flat or has a burst-suppression pattern under the influence of barbiturates, the possibility remains that their cerebral protective effect may be maximal when doses far in excess of those necessary to flatten the EEG are used. This possibility has not been explored in clinical practice.

In focal cerebral ischaemia, the somatosensory evoked potential (SEP) remains unaffected as local cerebral blood flow falls and declines sharply at a level of cerebral blood flow which is distinctly higher than that at which acute neuronal necrosis is seen. This makes them intrinsically suitable for intraoperative monitoring during the elective temporary occlusion of a cerebral artery, since there is a margin of safety in terms either of cerebral blood flow or of time before permanent damage occurs, and in which remedial or evasive action can be taken.

The technique of temporary occlusion of the parent artery of an intracranial aneurysm during the final stages of its dissection greatly facilitates this task by promoting partial or total collapse of the aneurysm and the immediately adjacent arterial structures. At the same time, normal perfusion of other areas of the brain and of the rest of the body is maintained, while the risk of intraoperative aneurysmal rupture, a potentially catastrophic event feared justifiably by neurosurgeon and neuroanaesthetist alike, is minimised.

Such a technique, however, demands that the viability of the areas subjected to ischaemia during the period of vascular occlusion be guaranteed. As already indicated, the SEP is suitable for monitoring in this situation provided that the areas most affected by the occlusion constitute part of the pathway of the SEP modality being monitored. Thus, the median nerve SEP is used to monitor the cerebral cortex rendered ischaemic by middle cerebral artery occlusion and the posterior tibial nerve SEP is used to monitor the cortex affected by anterior cerebral artery occlusion. Such monitoring is readily carried out in the presence of doses of barbiturates which produce a flat EEG.

Among 25 cases where cerebral aneurysm were clipped with the aid of

temporary vascular occlusion and moderate hypothermia, neurological complications were never seen postoperatively in the absence of gross changes in the SEP during the period of occlusion. Two minutes of middle cerebral artery occlusion continuing after loss of the median nerve SEP appear to be tolerated in these circumstances without neurological sequelae. The SEP was lost relatively early in cases undergoing early surgery, cases where a focal neurological deficit was present immediately preoperatively and in cases where a focal neurological deficit had been present transiently at the time of subarachnoid haemorrhage. These appear to constitute high risk groups from ischaemic damage during temporary vascular occlusion.

Upon loss of the SEP during temporary vascular occlusion, a period of reperfusion is desirable before reoccluding and continuing the dissection. Several periods of occlusion and reperfusion can be employed. If a long period of occlusion is anticipated in order to complete the dissection and clip the aneurysm while the SEP is lost early, the employment of additional cerebral protective measures should be considered. Appropriate SEP monitoring can be used in this way as an indicator for their use. Here, only hypothermia and barbiturates are considered in detail. However, free radical scavenging agents, other pharmaocological agents and fluorocarbons all offer possibilities for increasing the tolerance of the brain to a period of ischaemia, while meticulous attention to the maintenance of a high systemic arterial blood pressure, a normal to high arterial carbon dioxide tension and a low blood glucose level may contribute further to increasing tolerance to ischaemia during temporary cerebrovascular occlusion.

The middle cerebral artery occlusion times tolerated without neurological sequelae by our cases are strikingly longer than those reported at normal temperatures. This offers the surgeon, and the patient, far superior working conditions. Moderate hypothermia surely deserves serious reappraisal for use in this situation.

Samenvatting

Subarachnoidale bloeding komt in Nederland in ongeveer 8.7 per 100.000 inwoners per jaar voor. Van de patiënten met intracraniële aneurysmata die in de Neurochirurgische Kliniek van het Academisch Ziekenhuis Groningen voor operatie in aanmerking komen, is ca. 33% jonger dan 40 jaar, 62.5% jonger dan 50 jaar, en 90% minder dan 60 jaar oud. Een derde van alle patienten, die een subarachnoidale bloeding doormaken, overlijdt of heeft neurologische uitvalsverschijnselen na de bloeding. Bij 20% van de patienten die de bloeding overleven treedt binnen twee weken een recidief-bloeding op. Hoewel de vooruitgang in de operatieve techniek er in de afgelopen jaren toe bijgedragen heeft dat de operatieve mortaliteit in sommige centra tot 2% kon worden teruggebracht, is een belangrijk deel van de morbiditeit en mortaliteit bij patienten met een aneurysma van de hersenvaten gerelateerd aan de ontwikkeling van late ischaemische complicaties als gevolg van cerebrale vaatspasme. Deze kan zich manifesteren vanaf de vierde dag na de subarachnoidale bloeding en uitgelokt worden of verergeren door manipulatie tijdens de operatie, in het bijzonder wanneer het aneurysma tijdens de operatie scheurt. Vaatspasme kan wel gedurende vier weken aanhouden en ernstige vormen aannemen. Wanneer de door de ontwikkeling van een aanzienlijke mate van oedeem optredende cerebrale ischaemie of intracraniële hypertensie geen blijvende schade tot gevolg heeft, kan een goed resultaat na het verdwijnen van de vasospasme worden verwacht.

Terwijl er in de bestrijding van vasospasm ten tijde van het schrijven van dit proefschrift nog vrijwel geen vooruitgang is geboekt, wordt hier de ontwikkeling beschreven, in de tienjarige periode van 1977 tot 1987 in de Neurochirurgisch Kliniek van het Academisch Ziekenhuis Groningen, van technieken die tijdens operatie aangewend kunnen worden om de weerstand van de hersenen tegen ischaemie te verhogen, alsmede van een methode die het risico van intra-operatieve ruptuur van het aneurysma tot een minimum reduceert.

De maatregelen die tijdens operatie kunnen worden genomen om de weerstand van de hersenen tegen ischaemie te vergroten, vallen in grote lijnen in drie groepen uiteen:

I. *Hypothermie.* Wanneer de lichaamstemperatuur met 9°C wordt verlaagd, vermindert het zuurstofverbruik met de helft van dat bij de normale lichaamstemperatuur. In de jaren '60 werd hypothermie voor chirurgie van intracraniële aneurysmata op grote schaal toegepast, maar gebruik ervan als routine vindt heden nog maar in enkele centra plaats. In de Neurochirurgische Kliniek van het Academisch Ziekenhuis is hypothermie bij cerebrale vasculaire

chirurgie een gangbare procedure gebleven. De methode is dan ook toegepast bij al het klinische werk dat hier wordt beschreven. De waarde ervan wordt geïllustreerd aan een geval van overleving van één patiënt die, na meer dan 35 minuten hartstilstand, slechts geringe neurologische schade overhield. Voorts werd een techniek van tijdelijke vaatafsluiting ontwikkeld, die bij normale lichaamstemperatuur alleen in een veel beperktere vorm mogelijk zou zijn. Het valt te verwachten, dat er opnieuw belangstelling zal ontstaan voor hypothermie bij de chirurgie van cerebrale aneurysmata.

II. *Barbituraten* zijn al geruime tijd bekend als effectief middel voor de vermindering van hersenoedeem en de verhoogde druk die daar het gevolg van is. Resultaten van experimenteel onderzoek bij primaten en niet-primaten worden beschouwd, waarbij er aanwijzingen naar voren komen, dat barbituraten werkzaam zijn bij het verlichten van de gevolgen van focale cerebrale ischaemie, vooropgezet dat deze van korte duur is en de toediening wordt begonnen hetzij voor of heel kort na het optreden van de ischaemie. Dit effect wordt gezien bij afwezigheid van hersenoedeem en is dus onafhankelijk van enige maatregel die het oedeem vermindert. De werking is wel gerelateerd aan de toegediende dosis.

Naar aanleiding van het herstel van een patiënt met fulminant post-operatief hersenoedeem na afsluiting van een arteria cerebri anterior na behandeling met 32 g natrium-thiopentone, werd, in aanmerking genomen de kennelijk toenemende incidentie van post-operatieve complicaties en de bovengenoemde experimentele aanwijzingen, aan een serie van 33 opeenvolgende patiënten profylactisch barbituraat-medicatie toegediend. Natrium-thiopentone veroorzaakte hartritmestoornissen gedurende hypothermie, en wanneer het als enkelvoudige oplaaddosis werd gegeven voorafgaand aan de verlaging van de lichaamstemperatuur, was de werking te kort om de periode die nodig was om het aneurysma vrij te prepareren te overbruggen. Met Pentobarbitone daarentegen was de haemodynamische situatie stabiel en waren er geen ritmestoornissen, zodat de toediening tot aan het clippen van het aneurysma kon worden voortgezet.

De klinische resultaten van deze gevallen tonen voor het eerst de bescherming door barbituraten bij de mens aan. Het mechanisme van deze bescherming loopt namelijk niet via een vermindering van de intracraniele hypertensie die het gevolg zou zijn van een door de barbituraten verminderd hersenoedeem - en is wel volledig verenigbaar met experimentele waarnemingen bij primaten. Terwijl mortaliteit en blijvende morbiditeit samen bij patiënten met een aneurysma van de arteria cerebri media daalde van 5/8 tot 0/8, werd slechts een gering voordeel waargenomen bij aneurysmata van de arteria carotis, de arteria communicans posterior of the arteria communicans anterior. Eén patiënt met permanente afsluiting van de arteria cerebri media vond geen baat bij de behandeling. De beste resultaten, hoewel niet statistisch significant, werden gezien bij patiënten

die de hoogste doses kregen. Het minst bevredigend waren de resultaten bij de laagste doseringen. Het onttrekken van barbituraten bij aanwezigheid van vasospasme leidde tot het opnieuw optreden van hersenoedeem, soms in ernstige vorm.

III. *Neuromonitoring.* De controversiële vraag met betrekking tot de juiste dosering van barbituraten voor klinische doeleinden werd onderzocht door studie van registraties van de Cerebral Function Monitor (CFM) in die gevallen waarin barbituraten profylactisch werden toegediend. De CFM registratiecurves waren vlak gedurende het vrijprepareren van het aneurysma in de 24 gevallen waarin pentobarbitone werd toegediend. De spiegels van pentobarbitone in het serum waren niet consequent gerelateerd aan spontane corticale electrische activiteit, noch gedurende toediening van pentobarbitone of de uitscheiding daarvan, noch bij één enkele patiënt op verschillende tijdstippen, noch bij verschillende patiënten met een zelfde niveau van cerebrale activiteit. In aanwezigheid van een vlakke CFM-curve bleef bij alle patiënten een antwoord op de prikkel als gevolg van de operatie bestaan, soms vergezeld door acute hypertensie.

De implicaties van deze bevindingen worden ter discussie gesteld. Een dosis pentobarbitone, hoger dan nodig om een afvlakking van het EEG te bewerkstelligen, werd door alle patiënten bij een lichaamstemperatuur van 29°C goed verdragen. Wanneer de spontane electrische activiteit door barbituraten wordt uitgeschakeld betekent dit blijkbaar niet dat er een toestand van maximale functionele neuronale depressie is: zowel een response op de retractie als de aanwezigheid van verschillende modaliteiten van "evoked potentials" blijven behouden. De evoked potentials zijn daarom geschikt voor het bewaken van de hersenfunctie wanneer het EEG door barbituraten afgevlakt is: er is zelfs geen andere beoordeling mogelijk in deze situatie. Aangezien verder wordt beschreven, dat de beschermende werking van barbituraten afhankelijk is van de dosis, oplopend tot doseringen die veel hoger zijn dan nodig om het EEG af te vlakken, en dat de functionele neuronale depressie verre van maximaal is wanneer het EEG een burst-suppressie patroon heeft of juist is afgevlakt door de barbituraten, bestaat de mogelijkheid dat de beschermende werking maximaal zou kunnen zijn wanneer doseringen worden gebruikt die ver liggen boven die welke nodig zijn om het EEG vlak te maken. Deze mogelijkheid is niet klinisch onderzocht.

De somatosensorische evoked potentials blijven afhankelijk onveranderd wanneer de locale cerebrale circulatie afneemt, en dalen dan steil bij een niveau dat duidelijk hoger is dan het niveau waarop acute neuronale necrose wordt waargenomen. Dit maakt ze geschikt voor intra-operatieve bewaking gedurende de electieve afsluiting van een arterie. Er is immers een veiligheidsmarge wat betreft de grootte van de cerebrale perfusie en/of de tijd waarbinnen geen

blijvende schade optreedt, en waarin maatregelen ter behandeling of ter vermijding kunnen worden genomen.

De tijdelijke afsluiting van het aanvoerend bloedvat van een intra-craniëel aneurysma gedurende het laatste stadium van het vrijleggen ervan, vergemakkelijkt het vrij prepareren duidelijk doordat het aneurysma en de in de onmiddellijke omgeving daarvan gelegen arteriële structuren geheel of gedeeltelijk collaberen. Tegelijkertijd blijft een normale doorbloeding van andere gedeelten van de hersenen en de rest van het lichaam gehandhaafd. Het risico van een ruptuur van het aneurysma tijdens de operatie. iets dat wegens de mogelijke catastrofale gevolgen terecht door neurochirurg en neuroanaesthesist gevreesd wordt, is zo klein mogelijk gehouden. Een dergelijke techniek vereist echter, dat de levensvatbaarheid van die gebieden die blootstaan aan ischaemie gedurende de vaatafsluiting, wordt gegarandeerd. Zoals aangegeven zijn SEP's geschikt voor bewaking in deze situatie, vooropgesteld dat voor de gebieden die het meest door de afsluiting bedreigd worden de geëigende SEP modaliteit wordt gebruikt. Zo wordt de SEP van de nervus medianus gebruikt om de ischaemisch gemaakte hersenschors te controleren bij afsluiting van de arteria cerebri media, en de SEP van de nervus tibialis voor de cortex die betrokken is bij afsluiting van de arteria cerebri anterior. Deze bewaking is gemakkelijk uit te voeren bij een barbituraatdosis die een vlak EEG tot gevolg heeft.

Onder 25 gevallen waarin cerebrale aneurysmata werden geclipped met behulp van tijdelijke afsluiting van het aanvoerend vat en matige hypothermie, waren er postoperatief geen neurologische complicaties wanneer in de afklemmingsperiode geen grotere veranderingen in de SEP waren opgetreden. Een afsluiting van de arteria cerebri media van twee minuten na verlies van de SEP van de nervus medianus lijkt onder deze omstandigheden zonder neurologische gevolgen te worden verdragen. De SEP verdween betrekkelijk vroeg in gevallen van operatie in een vroeg tijdstip, in gevallen waarin direct pre-operatief focale neurologische uitval bestond, en in die gevallen waarin ten tijde van de subarachnoidale bloeding focale neurologische uitval van voorbijgaande aard had bestaan.

Bij het wegvallen van de SEP gedurende tijdelijke vaatocclusie, is het wenselijk een periode van reperfusie in te lassen voordat opnieuw afsluiting en dissectie plaatsvindt. Er kunnen verscheidene periodes van afsluiting en reperfusie worden toegepast. Wanneer een lange periode van afsluiting wordt verwacht ten einde het aneurysma vrij te prepareren en een clip te plaatsen, moet de toepassing van andere beschermende maatregelen worden overwogen. Bewaking met SEP kan zo een indicatie geven voor het gebruik hiervan. Hier worden alleen hypothermie en barbituraten in detail beschouwd. Middelen die z.g. vrije radicalen wegvangen, andere farmaca en fluorcarbons hebben alle de mogelijkheid de tolerantie van de hersenen voor een periode van ischaemie te

vergroten, terwijl ook nauwgezette aandacht voor het op peil houden van een hoge systemische bloeddruk, een normale tot hoge CO_2-spanning en een laag bloedglucosegehalte een belangrijke bijdrage leveren.

De tijd gedurende welke de arteria cerebri media bij onze patiënten kon worden afgesloten zonder dat neurologische gevolgen optraden is opvallend langer dan wordt opgegeven bij normale lichaamstemperatuur. Dit biedt voor chirurg en patiënt duidelijke voordelen. Matige hypothermie verdient voor toepassing in deze situatie dan ook stellig herwaardering.

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